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SOLANUM BULBOCASTANUM LATE BLIGHT RESISTANCE GENE AND USE THEREOF

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CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/407,100, filed August 29, 2002. The disclosure of said provisional application is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0002] The present invention is directed to pathogen resistance in plants. More particularly, the invention is directed to identification and use of a gene that provides resistance to late blight disease. Even more particularly, the invention is directed to a *Solanum bulbocastanum* late blight resistance gene, nucleic acid molecules encoding polypeptides which confer resistance to late blight, and methods of using the gene, including expression in plant cells to confer or enhance a plant's resistance to late blight.

2. Description of the Art

[0003] On a worldwide basis, late blight, caused by the fungus *Phytophthora infestans*, is the most important of potato diseases. Worldwide losses due to potato late blight are estimated to be about $3 billion annually. Conservatively, *P. infestans* costs the potato industry in the United States $200 to $400 million annually.

[0004] Currently, late blight is controlled by application of fungicides. The cost of chemical control in the U.S., now applied in essentially all potato producing regions, is approximately $100-$200 per acre. Given that approximately 1.2 million acres are planted to potatoes annually in the U.S., the control costs alone are significant. In addition, in many years storage losses due to this pathogen are in the same range as the cost of control.

[0005] In the U.S., the recent migration from Mexico of highly aggressive and virulent new forms of *P. infestans* poses a serious threat to all potato producing regions. In particular, the presence of A2 mating type and fungicide resistant forms in field populations of the fungus limits producers' options in control practices.

[0006] *P. infestans* also causes late blight in other crops, including tomato, eggplant, and other solanaceous species. The new, aggressive strains of *P. infestans* also represent a serious threat to commercial tomato production.

[0007] Identification of a late blight resistance gene and development of transgenic plants resistant to *P. infestans*, is important goal in plant research to reduce crop losses and to reduce the need for fungicide application and costs of chemical control.

[0008] A wide variety of genetic loci that confer resistance to pathogens have been identified in plant species. These resistance loci often encode dominant resistance genes, or R genes. The R genes confer either vertical race-specific or horizontal nonspecific resistance to a pathogen (Plank, 1968). Vertical resistance is based upon an induced hypersensitive response in which the pathogen infection is contained by localized host cell death at infection sites. The mechanism for vertical resistance has been proposed to involve activation of the cell death response when a specific plant receptor (the R gene product) interacts with an elicitor produced by a corresponding Avr gene in the invading pathogen (Flor, 1971). Pathogen races are defined by distinct Avr gene profiles and resistance results from the interaction between specific R gene and Avr gene products (the gene for gene interaction).

[0009] In contrast to vertical resistance, horizontal resistance generally involves multiple plant genes and provides a general, stable, pathogen resistance in a race-nonspecific manner. Horizontal resistance is not correlated with the hypersensitive response, involving instead limiting pathogen spread in the host. *Solanum bulbocastanum* contains a dominant R gene locus which confers horizontal resistance to *P. infestans* when introgressed into the cultivated potato (Naess *et al.*, 2000; Naess *et al.*, 2001).

[0010] Map-based cloning has been employed to identify a variety of R genes from crop plants (Ballvora *et al.*, 2002; Brueggeman *et al.*, 2002; Dixon *et al.*, 1996; Feuillet *et al.*, 1997; Lagudah *et al.*, 1997; Ori *et al.*, 1997; Yoshimura *et al.*, 1998).

SUMMARY OF THE INVENTION

[0011] We have now isolated a gene from the wild potato species *Solanum bulbocastanum* which confers horizontal resistance to *Phytophthora infestans*, the fungal pathogen that causes late blight disease. cDNA and genomic DNA sequences of the *Solanum bulbocastanum* late blight resistance gene, hereinafter denoted as *Sbul1*, are specifically exemplified herein (SEQ ID NO:1 and 3, respectively). The deduced amino acid sequence is shown in SEQ ID NO:2 and 4. The resistance protein is in the class of Nucleotide Binding Site-Leucine-Rich Repeat Proteins (NBS-LRRP), and the gene in *S. bulbocastanum* is flanked by related NBS-LRRP gene sequences.

[0012] DNA encoding the resistance protein has been introduced into potato plants and confers resistance to *P. infestans*. A comparison of the deduced amino acid sequence of *Sbul1*, which confers late blight resistance in transgenic plants, and the deduced amino acid sequence encoded by the *S. bulbocastanum* gene denoted herein as *Sbul2*, which does not confer resistance, reveals 101 differences between the two proteins over 989 residues, or 90% identity. A comparison of the nucleic acid sequences of *Sbul1* and *Sbul2* reveals 221 differences between the two genes over 3174 bp of coding sequence, or 93% identity.

[0013] Accordingly, the invention is directed to nucleic acid molecules encoding a pathogen resistance gene, the gene being characterized in that it encodes the amino acid sequence shown in SEQ ID NO:4, or an amino acid sequence showing greater than about 90% sequence identity with SEQ ID NO:4 and which encodes a polypeptide having ability to confer or enhance a plant's resistance to late blight. Exemplary nucleic acid molecules include the exemplified cDNA and genomic DNA sequences and nucleic acid sequences

having greater than about 93% sequence identity with the coding domain of the exemplified sequences and which confer or enhance a plant's resistance to late blight.

[0014] The invention is also directed to recombinant nucleic acid molecules containing the sequences encoding the polypeptides which confer late blight resistance, including, for example, recombinant vectors, such as cloning, expression or transformation vectors.

[0015] Another aspect of the invention is the provision of cells which are transformed by the vectors or DNA sequences of the invention.

[0016] Methods of using the sequences are also encompassed by the invention. A particular use of the invention is the provision of plants or plant cells transformed with one or more nucleic acid sequences encoding a polypeptide which confers late blight resistance to provide plants having resistance to *P. infestans*, or to provide plants having enhanced resistance to *P. infestans* or related plant pathogens. Such plants include, for example, solanaceous plants. Prominent food crops are in the *Solanaceae* family. These include potato (*Solanum tuberosum*); tomato (*Lysopersicon*, e.g., *L. lycopersicum* and *L. esculentum*); pepper (*Capsicum*); eggplant (*Solanum melongena*). Most preferably, in the practice of the invention, the solanaceous plant is potato.

[0017] As described below, the locus containing the resistance gene was characterized by map-based cloning and chromosome walking using a *S. bulbocastanum* Bacterial Artificial Chromosome (BAC) library. The actual resistance gene was isolated using Polymerase Chain Reaction (PCR) as the allele of the locus which contains the gene was not represented in the library. Chimeric transgenes constructed with *Sbul1* transcribed from a potato ubiquitin (*Ubi3*) promoter were introduced into a susceptible potato variety. Greenhouse tests confirmed that transgenic potato clones containing these transgenes are resistant to late blight.

[0018] Accordingly, it is an object of the invention to provide nucleic acid sequences encoding polypeptides that confer late blight resistance; isolated polypeptides having this

activity; recombinant nucleic acid molecules including expression vectors encoding the polypeptides; and cells harboring the recombinant nucleic acid molecules or expression vectors.

[0019] It is also an object of the invention to provide transformation vectors comprising a recombinant molecule, which vectors are effective for stably introducing the recombinant molecule into a plant.

[0020] It is also an object of the invention to provide methods of producing and using polypeptides conferring late blight resistance.

[0021] It is another object of the invention to provide transgenic plants having resistance to late blight or related pathogen, wherein the resistance is a result of expression of a recombinant nucleic acid molecule of the invention. An important aspect is the conferral of horizontal resistance to late blight, thereby providing general rather than race-specific control of the pathogen.

[0022] A further aspect of the invention is the provision of oligonucleotide probes capable of detecting a late blight resistance gene or functional equivalents thereof and the use of the probes to isolate nucleic acid sequences encoding a late blight resistance polypeptide or functional equivalent thereof.

[0023] A major impact of this invention on agriculture will be in controlling *P. infestans* in potatoes. The introduction of the resistance gene into cultivated potatoes would be expected to significantly reduce costs of chemical control, as well as providing a novel method for controlling fungicide resistant pathogen populations.

[0024] An additional application of this invention is controlling late blight in other solanaceous plants, for example, tomato production. The new, aggressive strains of *P. infestans* also represent a serious threat to commercial tomato production. Introduction of this resistance gene into tomato will result in significant savings in chemical control of the pathogen in this commodity.

[0025] Other objects and advantages of the invention will become readily apparent from the ensuing description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] FIG. 1 shows the genetic map of the *S. bulbocastanum* late blight resistance gene locus. The approximate position of the locus is indicated by R. The positions of several RFLP markers relative to this locus are indicated. The relative positions of AFLP markers flanking the R gene are indicated.

[0027] FIG. 2 shows the assembly of an approximately 600 kb contig on *S. bulbocastanum* anchored by a BAC clone hybridizing to the RFLP marker CD60. BAC C29 was cloned by hybridization of filters to the labeled RFLP marker. BAC end-sequence analysis allowed design of specific primer pairs for both ends of the insert (F and R indicate forward and reverse). For each walk subsets of the BAC library were pooled and screened by PCR using these specific primers. BAC end-sequence analysis also revealed the position of members of a family of nucleotide binding site-leucine-rich repeat proteins (NBS-LRRP) indicated.

[0028] FIG. 3 shows the structure of the *S. bulbocastanum* chromosome 8 NBS-LRRP domain linked to late blight resistance. The domain contains six complete and three partial NBS-LRRP coding sequences. Only two of the six complete genes on the BAC contig, *Sbul2* and *Sbul3*, were found to encode uninterrupted open reading frames. The remaining four NBS-LRRP genes are interrupted by frame shift mutations (NBS Sal 37-1 and *Sbul1*) or stop codons (NBS Sal 37-3 and NBS 24K).

[0029] FIG. 4 shows the structure of the *Sbul1* transgenes. *Sbul1* genomic (SEQ ID NO:3) and cDNA (SEQ ID NO:1) sequences were fused to promoter and terminator sequences from the potato *Ubi3* gene (Garbarino *et al.*, 1994a; Garbarino *et al.*, 1994b).

[0030] FIG. 5 shows transgenic potatoes expressing *Sbul1* genomic and cDNA transgenes have improved resistance to *P. infestans* US8. Detached leaves of greenhouse-grown

transgenic and control plants were inoculated with *P. infestans* and incubated for four days. Lesion size determined computationally (Bioquant Systems).

[0031] FIG. 6 shows a comparison of the deduced amino acid sequences of *Sbul1*, which confers late blight resistance in transgenic plants, and *Sbul2* which does not. Comparison reveals 101 differences between the two proteins over 989 residues, or 90% identity.

[0032] FIG. 7 shows a comparison of the nucleic acid sequences of *Sbul1*, which confers late blight resistance in transgenic plants, and *Sbul2* which does not. Comparison reveals 221 differences between the two genes over 3174 bp of coding sequence, or 93% identity

[0033] FIG. 8 shows potato lines transformed with the *Sbul1* genomic transgene have enhanced resistance to *P. infestans* US8 in intact plant assays.

BRIEF DESCRIPTION OF THE SEQUENCES

[0034] SEQ ID NO:1 shows the cDNA sequence of the *Solanum bulbocastanum* late blight resistance gene *Sbul1*. Sequence feature information: *Solanum bulbocastanum Sbul1* cDNA sequence: nucleotide 1 to 3193; coding region: nucleotide 52 to 3018; translation initiation codon: nucleotide 52 to 54; translation termination codon: nucleotide 3016 to 3018.

[0035] SEQ ID NO:2 shows the amino acid sequence encoded by SEQ ID NO:1.

[0036] SEQ ID NO:3 shows the DNA sequence of the active *Sbul1* gene, a PCR product using template DNA from a late blight-resistant back cross 3 potato line containing *S. bulbocastanum* DNA. The sequence contains a 412 bp intron. Sequence feature information: *Solanum bulbocastanum* genomic *Sbul1* sequence: nucleotide 1 to 3595; coding region: first coding domain : nucleotide 57 to 487; second coding domain: nucleotide 900 to 3435, wherein the 5' end of the second domain is linked to the 3' end of the first domain; intron: nucleotide 488 to 899; translation initiation codon: nucleotide 57 to 59; translation termination codon: nucleotide 3433 to 3435.

[0037] SEQ ID NO:4 shows the amino acid sequence encoded by SEQ ID NO:3.

[0038] SEQ ID NO:5 shows the DNA sequence of the *Sbul2* gene. Sequence feature information: *Solanum bulbocastanum* genomic *Sbul2* sequence: nucleotide 1 to 3347; coding region: first coding domain: nucleotide 57 to 509; second coding domain: nucleotide 789 to 3347, wherein the 5' end of the second domain is linked to the 3' end of the first domain; intron: nucleotide 510 to 788; translation initiation codon: nucleotide 57 to 59; translation termination codon: nucleotide 3345 to 3347.

[0039] SEQ ID NO:6 shows the amino acid sequence encoded by SEQ ID NO:5.

[0040] SEQ ID NO:7 shows the DNA sequence of the *Sbul3* gene. Sequence feature information: *Solanum bulbocastanum* genomic *Sbul3* sequence: nucleotide 1 to 3222; coding region: first coding domain : nucleotide 58 to 528; second coding domain: nucleotide 691 to 3222, wherein the 5' end of the second domain is linked to the 3' end of the first domain; intron: nucleotide 529 to 690; translation initiation codon: nucleotide 58 to 60; translation termination codon: nucleotide 3220 to 3222.

[0041] SEQ ID NO:8 shows the amino acid sequence encoded by SEQ ID NO:7.

[0042] SEQ ID NO:9 shows the sequence of the chimeric *Ubi3/Sbul1* genomic transgene. Sequence feature information: *Ubi3-Solanum bulbocastanum* genomic *Sbul1-Ubi3* sequence: nucleotide 1 to 5028; Potato *Ubi3* promoter: nucleotide 1 to 953; *Solanum bulbocastanum* genomic *Sbul1* gene: nucleotide 973 to 4566; coding region: first coding domain : nucleotide 1029 to 1459; second coding domain: nucleotide 1872 to 4407, wherein the 5' end of the second domain is linked to the 3' end of the first domain; intron: nucleotide 1460 to 1871; translation initiation codon: nucleotide 1029 to1031; translation termination codon: nucleotide 4405 to 4407.

[0043] SEQ ID NO:10 shows the amino acid sequence encoded by SEQ ID NO:9.

DEFINITIONS

[0044] Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this invention belongs.

The following references provide one of skill with a general definition of many of the terms used in this invention: Singleton, *et al.*, DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY (2d ed. 1994); THE CAMBRIDGE DICTIONARY OF SCIENCE AND TECHNOLOGY (Walker ed., 1988); THE GLOSSARY OF GENETICS, 5TH ED., Rieger, R., *et al.* (eds.), Springer Verlag (1991); and Hale & Marham, THE HARPER COLLINS DICTIONARY OF BIOLOGY (1991). References providing standard molecular biological procedures include Sambrook *et al.* (1989) *Molecular Cloning*, second edition, Cold Spring Harbor Laboratory, Plainview, NY; *DNA Cloning*, Vols. I and II, IRL Press, Oxford, UK; and Hames and Higgins (eds.) (1985) *Nucleic Acid Hybridization,* IRL Press, Oxford, UK. References related to the manipulation and transformation of plant tissue include Kung and Arntzen (eds.) (1989) *Plant Biotechnology*, Butterworths, Stoneham, MA; R. A. Dixon (ed.) (1985) *Plant Cell Culture: A Practical Approach*, IRL Press, Oxford, UK; Schuler and Zielinski (1989) *Methods in Plant Molecular Biology*, Academic Press, San Diego, CA; Weissbach and Weissbach (eds.) (1988) Academic Press, San Diego, CA; I. Potrykus (1991) *Ann. Rev. Plant Physiol. Plant Mol. Biol.* 42:205; Weising *et al.* (1988) *Annu. Rev. Genet.* 22:421; van Wordragen et al. (1992) *Plant Mol. Biol. Rep.* 19:12; Davey et al. (1989) *Plant Mol. Biol.* 13:273; Walden and Schell (1990) *Eur. J. Biochem.* 192:563; Joersbo and Brunstedt (1991) *Physiol. Plant.* 81:256 and references cited in those references. The references cited in the list of References attached below also provides a description of the terms used herein. The following U.S. patents are incorporated herein by reference: U.S. Patents Nos. 5,589,339; 6,084,156; 6,225,527; 6,287,865; 6225,532; 6,287,865; 6,100,449; and published application PCT/US00/23802 (WO 01/16353). All references cited in the present application are expressly incorporated by reference herein.

DETAILED DESCRIPTION OF THE INVENTION

[0045] We have now cloned a horizontal late blight resistance gene from *S. bulbocastanum*. As described below, the resistance gene *Sbul1* was isolated by map-based cloning. In this technique the locus that confers resistance is mapped relative to amplified fragment length

polymorphism (AFLP) and restriction fragment length polymorphism (RFLP) markers that are linked to the resistance gene. Four markers that appeared to be most closely linked to the resistance gene were used to probe a *S. bulbocastanum* genomic bacterial artificial chromosome (BAC) library and hybridizing BAC clones identified. The resistance locus was obtained by chromosome walking from an original anchor clone. The resistance gene was identified by introduction of candidate genes from the locus into transgenic potato and screening for late blight resistance.

[0046] The present invention is directed to isolated nucleic acid sequences derived from a *S. bulbocastanum* gene which encode polypeptides which confer horizontal late blight resistance. The specifically exemplified nucleic acid sequences include the *Sbul1* cDNA sequence (SEQ ID NO:1) and the DNA sequence of the active *Sbul1* gene, a PCR product using template DNA from a late blight-resistant back cross 3 potato line containing *S. bulbocastanum* DNA (SEQ ID NO:3). The latter sequence contains a 412 bp intron. SEQ ID NO:4 shows the deduced amino acid sequence of the *Sbul1* gene product. The invention encompasses nucleic acid sequences which have greater than about 93% sequence identity with the coding domain of the exemplified sequences and encode a polypeptide which confers or enhances a plant's resistance to late blight. More preferably, the nucleic acid sequences have about 95% sequence identity with the coding domain of the exemplified sequences and encode a polypeptide which confers or enhances a plant's resistance to late blight. For purposes of the present invention, the degree of identity between two nucleic acid sequences is determined any method know in the art, for example by the Clustal method (Thompson *et al.* 1994), using ClustalW 1.7 or 1.8 (http://dot.imgen.bcm.tmc.edu:9331/multi-align/multi-align.html). Further, nucleic acid sequences which hybridize under high stringency conditions with the coding region of the DNA sequence of SEQ ID NO:1 or 3 and which encode a polypeptide having the activity defined above, are also encompassed by the present invention.

[0047] The invention is directed to nucleic acid molecules encoding the amino acid sequence of SEQ ID NO:4, or an amino acid sequence showing greater than about 90% sequence identity with SEQ ID NO:4 and which encodes a polypeptide having ability to confer or enhance a plant's resistance to late blight. More preferably, the encoded amino acid sequence has at least about 95%, and most preferably at least about 97% sequence identity with SEQ ID NO:4 and has the activity defined above. For purposes of the present invention, the degree of identity between two amino acids is determined any method known in the art, for example, by the FASTA/FASTP method of Pearson (1990), using ALIGN (http://dot.imgen.bcm.tmc.edu:9331/seq-search/alignment.html), with the BLOSUM50 or PAM250 scoring matrix.

[0048] Preferably, the polypeptides of the present invention comprise an amino acid sequence of SEQ ID NO:4 or an amino acid sequence showing greater than about 90% sequence identity with SEQ ID NO:4 and which encodes a polypeptide having ability to confer or enhance a plant's resistance to late blight.

[0049] The degeneracy of the genetic code is well known to the art; therefore, synonymous coding sequences with one or more codon substitutions can be readily determined by one of ordinary skill in the art. Synonymous coding sequences vary from the exemplified coding sequences but encode proteins of the same amino acid sequences as those specifically provided herein. Examples of conservative substitutions are within the groups of basic amino acids (such as arginine, lysine and histidine), acidic amino acids (such as glutamic acid and aspartic acid), polar amino acids (such as glutamine and asparagine), hydrophobic amino acids (such as leucine isoleucine and valine), aromatic amino acids (such as phenylalanine, tryptophan and tyrosine), and small amino acids (such as glycine, alanine, serine, threonine and methionine). Amino acid substitutions which do not generally alter the specific activity are known in the art as described, for example, by H. Neurath and R. L. Hill, 1979, *In, The Proteins*, Academic Press, New York. The most commonly occurring exchanges are Ala/Ser,

Val/Ile, Asp/Glu, Thr/Ser, Ala/Gly, Ala/Thr, Ser/Asn, Ala/Val, Ser/Gly, Tyr/Phe, Ala/Pro, Lys/Arg, Asp/Asn, Leu/Ile, Leu/Val, Ala/Glu, and Asp/Gly as well as these in reverse.

[0050] The present invention also relates to recombinant expression vectors comprising a nucleic acid sequence of the present invention, a promoter, and transcriptional and translational stop signals.

[0051] The present invention also relates to recombinant host cells, comprising a nucleic acid sequence of the invention, which are advantageously used in the recombinant production of the polypeptides. Preparation of transformed host cells and cloning methods are described by U.S. Patent No. 5,374,540, which is incorporated herein by reference.

[0052] Preparation of Transgenic Plants: The transgenic plant or plant cell expressing an RNA transcript or polypeptide of the present invention may be constructed in accordance with methods known in the art. In brief, the plant or plant cell is constructed by incorporating one or more expression constructs encoding a polypeptide of the present invention into the plant host genome and propagating the resulting modified plant or plant cell into a transgenic plant or plant cell.

[0053] As discussed above, a particular use of the invention is the provision of plants or plant cells transformed with a DNA sequence encoding an amino acid sequence which confers resistance to late blight or related pathogens.

[0054] Another use of the invention is as probes and primers capable of detecting a late blight resistance gene or functional equivalent thereof in fungi of the genus *Phytophthora*. Using the nucleic acid sequences of the invention facilitates the isolation of homologous genes from hosts to obtain genes which protect host cells, including fungi and plants against other fungal pathogens.

EXAMPLES

[0055] The following examples are intended only to further illustrate the invention and are not intended to limit the scope of the invention.

Map-based cloning of the *S. bulbocastanum* late blight resistance gene (*Sbul1*)

[0056] *S. bulbocastanum* DNA was introgressed into potato by somatic fusion at the University of Wisconsin (Naess *et al.*, 2001). Fertile progeny were then back crossed to potato. The position of the *S. bulbocastanum* late blight resistance gene locus was mapped using a back-cross 3 population segregating for *P. infestans* resistance using a combination of AFLP (Vos *et al.*, 1995) and RFLP techniques. The late blight resistance locus maps to chromosome 8 (Naess *et al.*, 2001). The segregating population was subjected to AFLP mapping, exhaustion of the commercially available primer/enzyme sets resulted in identification of over 400 polymorphic bands. RFLP mapping was also employed, the population was screened with a variety of chromosome 8 markers. The relative positions of the AFLP and RFLP markers closest to the *Sbul1* locus are shown in FIG. 1. The clustering of these markers, together with the failure of AFLP to generate a marker within the flanking RFLP probes (CD60 and TG261) suggested that the resistance locus is located in an area of chromosome 8 with high rates of recombination resulting in very different genetic and physical maps. This interpretation suggested that additional mapping was unnecessary, and four RFLP markers (TG282, TG505, CD60, PPOIII) were selected to probe a *S. bulbocastanum* BAC library (Song *et al.*, 2000).

Identification of Candidate *Sbul1* genes.

[0057] BAC clones corresponding to each of the four RFLP markers were isolated and used to anchor PCR-based chromosome walking (FIG. 1). BAC end-sequences were used to generate specific primer pairs for screening of pooled BAC clones by PCR (Cai *et al.*, 1995). The assembly of an approximately 600 kb contig proximal to the CD60 RFLP marker on *S. bulbocastanum* chromosome 8 is shown in FIG. 2. Computational (BLAST) alignment of the end sequences of BAC isolates C29F2F2R1 and C29F2F2R2 with the available database (Altschul *et al.*, 1990) indicated the presence of sequences encoding nucleotide binding site-leucine-rich repeat proteins (NBS-LRRPs) similar to previously identified R genes (Ballvora *et al.*, 2002; Lagudah *et al.*, 1997; Simons *et al.*, 1998; Yoshimura *et al.*, 1998). Primers

specific to the NBS-LRRP locus on the contig in FIG. 2 were employed in PCR screening of genomic DNA from the original population segregating for late blight resistance, and this locus was found to be linked to the resistance phenotype.

[0058] An approximately 75 kb region containing six complete NBS-LRRP genes was characterized. As shown in FIG. 3, four of the six complete genes were found to represent pseudogenes, with coding sequences interrupted by either frame shift mutations or stop codons. These data suggested that late blight resistance at this locus was associated with *Sbul2* and/or *Sbul3* expression.

Identification of the *Sbul1* late blight resistance gene.

[0059] Experiments to determine the efficacy of either *Sbul2* or *Sbul3* (FIG. 3) in conferring late blight resistance were based on mobilization of these genes plus at least 3 kb of 5' and 3' flanking sequence into susceptible potatoes by *Agrobacterium*-mediated transformation. *Sbul2* or *Sbul3* and flanking sequences were mobilized into a binary transformation vector pCGN1547 (McBride *et al.*, 1990). These binary vector constructs were used to introduce the *Sbul2* or *Sbul3* genes into potato varieties Lenape (Akeley *et al.*, 1968) and Atlantic (Webb *et al.*, 1978) by a standard transformation/selection protocol (Snyder *et al.*, 1993). Transgenic potato plants containing either the *Sbul2* or *Sbul3* genes were screened for resistance to late blight by detached leaf assay (Trognitz *et al.*, 1995). Neither the *Sbul2* or *Sbul3* genes conferred resistance to *P. infestans.*

[0060] The similarity of the NBS-LRRPs on the *S. bulbocastanum* contig (FIG. 3) to known disease resistance genes is significant. A BLAST database search (Altschul *et al.*, 1990) using the deduced amino acid sequence of *Sbul2* returns seven putative resistance genes from *Arabidopsis* at the highest identity ($P(N)<10^{-120}$) followed by the *I2 Fusarium oxysporum* resistance gene from tomato (Simons *et al.*, 1998) ($P(N)<10^{-108}$). In addition, this PCR probes from this locus indicate linkage to the resistance gene in the segregating population. It therefore appeared possible that one or more of the four pseudogenes present

on the *S. bulbocastanum* contig (FIG. 3) represented an inactive allele of a gene active on the other chromosome of this diploid species. Specific primers were prepared to the *Sbul1, Sbul2*, and *Sbul3* genes on the locus, and RACE (Rapid Amplification of cDNA Ends)-PCR was employed to amplify potential mRNAs from polyA$^+$ RNA prepared from *P. infestans*-infected *S. bulbocastanum* leaves. Messenger RNA products corresponding to *Sbul1*, *Sbul2* and *Sbul3* were amplified. This suggested that active *Sbul1* was heterozygous in *S. bulbocastanum*, with one allele active and the other interrupted by a frame shift mutation (Helgeson *et al.*, 1988). PCR amplification of *Sbul1* using genomic DNA from a late blight-resistant BC3 line as a template generated an amplified product encoding a mRNA essentially identical to the *Sbul1* cDNA (SEQ ID NO:3).

[0061] The DNA sequence of the active *Sbul1* cDNA is shown in SEQ ID NO:1. The deduced amino acid sequence is shown in SEQ ID NO:2. The DNA sequence of active *Sbul1* gene, a PCR product from *S. bulbocastanum*-containing potato genomic DNA, containing a 412 bp intron is shown in SEQ ID NO:3. The deduced amino acid sequence of the *Sbul1* gene product is shown in SEQ ID NO:4. The DNA sequence of the *Sbul2* gene is shown in SEQ ID NO:5, and the deduced *Sbul2* amino acid sequence is shown in SEQ ID NO:6. The DNA sequence of the *Sbul3* gene is shown in SEQ ID NO:7, and the deduced *Sbul3* amino acid sequence is shown in SEQ ID NO:8.

Expression of *Sbul1* in transgenic plants

[0062] In order to express *Sbul1* in transgenic plants two chimeric transgenes were constructed. Transcription of the *Sbul1* gene is directed from the potato *Ubi3* promoter, which will result in constitutive moderate-level expression (Garbarino *et al.*, 1994a; Garbarino *et al.*, 1994b). The *Ubi3* polyadenylation signal was fused to the 3' end of each sequence (FIG. 4).

[0063] The sequence of the genomic chimeric transgene is shown in SEQ ID NO:9. The transgenes shown in FIG. 4 were mobilized into the binary transformation vector pBINPLUS-

ARS. This vector is a version of the pBINPLUS vector (Van Engelen *et al.*, 1995) modified in our laboratory by replacement of selectable marker transcriptional control sequences (CaMV35S promoter, NOS terminator) with a promoter and terminator derived from the potato *Ubi3* gene (Garbarino *et al.*, 1994a). These binary vector constructs were used to introduce the transgenes into potato varieties Lenape (Akeley *et al.*, 1968) and Atlantic (Webb *et al.*, 1978) by a standard transformation/selection protocol (Snyder *et al.*, 1993). Transgenic potato plants were screened for resistance to late blight by detached leaf assay (Trognitz *et al.*, 1995).

Greenhouse assay of late blight resistance of transgenic potatoes expressing *Sbul1* transgenes

[0064] To assay for late blight resistance fully developed leaves from greenhouse-grown plants were detached. Inocula were obtained from two-week-old cultures of *P. infestans* (strain US8, Florida isolate) grown on rye agar. Inoculations were made by placing a 10ul droplet of a sporangial suspension (4 x 10^4 ml) that had been incubated at 8° C for 2.5 hours (to liberate zoospores) on both sides of the midrib of the abaxial surface. The inoculated leaflets were placed in petri dishes containing moistened filter paper to maintain 100% relative humidity. Inoculated material was incubated for 1 day at 15°C in darkness, then for four days at 15°C, 16-hour/day photoperiod (400 $E\text{-}^{m\text{-}2}S^{-1}$). A computer-driven image analysis system (Bioquant IV, R and M Biometrics, Nashville, TN) was used to obtain measurements of lesions. The lesion diameter was determined by projecting the whole leaves onto a grid lining the Bioquant Digitizing Pad. The digitizing pad was coupled with an IBM PC and measurements were generated using Bioquant Systems software.

[0065] As shown in FIG. 5, both the *Sbul1* genomic and cDNA transgenes conferred resistance to *P. infestans* in transgenic potatoes. As shown in FIG. 6, the deduced amino acid sequence of the *Sbul2* gene, which does not confer resistance, has 90% identity to the *Sbul1* deduced amino acid sequence. As shown in FIG. 7, the nucleic acid sequences of the *Sbul1* and *Sbul2* coding domains are 93% identical.

[0066] The data presented in FIG. 5 shows that *Sbul1*, when introduced into susceptible potato varieties, is capable of conferring resistance to late blight. While the *Sbul2* and *Sbul3* genes do not, individually, confer a resistant phenotype, this does not preclude a role for these gene products in enhancing *Sbul1*-mediated resistance originating from this locus.

Whole-plant glasshouse test of late blight resistance of potato plants transformed with *Sbul1*.

[0067] To assay for late blight resistance, transgenic and control tubers were planted in 6 inch pots and grown 16 hr light and 8 hr dark photoperiod using high pressure sodium lamps as supplemental lighting. Transgenic lines used in these experiments contained the genomic *Sbul1* transgene (SEQ ID NO:9). Inocula were obtained from cultures of *P. infestans* (strain MD-02-pet-1 an A2, US-8 genotype) grown in lima bean media in the dark at room temperature. After two weeks of incubation, the plates were flooded 2x with sterile water and scraped lightly using an L-shaped glass or plastic rod to collect sporangia. The liquid from the plates were filtered into a 1 liter glass beaker using two layers of cheesecloth. The total volume was roughly estimated and sporangia was counted using a hemacytometer. Using sterile water, the volume of the inoculum was adjusted that gave a final count of 5,000 sporangia/ml. The inoculum was transferred into a sprayer (approximately 2 ml/sec) and incubated at 4°C for 1 hour followed by room temperature incubation for 30 minutes.

[0068] The whole-plant glasshouse test described by Stewart et al. (1983) was used to determine which of the plants were resistant to *P. infestans*. Plants of each clone in flower bud were inoculated with *P. infestans*. Each plant was scored daily using Malcolmson's scoring scale of increasing resistance (Cruickshank et al., 1982) starting 7 days after inoculation, and plants of each clone compared. As shown in FIG. 8, two of the transgenic lines exhibited no infection 24 days after inoculation, six additional transgenic lines had intermediate levels of resistance.

Description of Plasmids

[0069] The plasmid pBT1596 consists of the *Sbul1* genomic transgene shown in SEQ ID NO:9 inserted into the multiple cloning site of the binary transformation vector pBINPLUS-ARS. The plasmid pBT1593 consists of the *Sbul1* cDNA sequence (SEQ ID NO:1) inserted between the potato *Ubi3* promoter and terminator sequences indicated in SEQ ID NO:9 in the multiple cloning site of the binary transformation vector pBINPLUS-ARS.

Statement of Deposit

[0070] The plasmids were introduced into the host *Escherichia coli* DH5α and the transformed *Escherichia coli* strains were deposited August 18, 2003 under terms of the Budapest Treaty with Agricultural Research Service Culture Collection (NRRL) National Center for Agricultural Utilization Research, Agricultural Research Service, U.S. Department of Agriculture, 1815 North University Street, Peoria, Illinois 61604 USA and given the following accession numbers:

Plasmid	Accession No.	SEQ ID NO
pBT1596	NRRL B-30685	SEQ ID NO:9
pBT1593	NRRL B-30686	SEQ ID NO:1

[0071] It is understood that the foregoing detailed description is given merely by way of illustration and that modification and variations may be made within, without departing from the spirit and scope of the invention. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety.

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SEQUENCE LISTING

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Ala Lys Leu Arg Gln Val Leu Lys Val Gly Ala Ser Gly Ala Ser Val
275 280 285

Leu Thr Thr Thr Arg Leu Glu Lys Val Gly Ser Ile Met Gly Thr Leu
290 295 300

Gln Pro Tyr Glu Leu Ser Asn Leu Ser Gln Glu Asp Cys Trp Leu Leu
305 310 315 320

Phe Met Gln Arg Ala Phe Gly His Gln Glu Glu Ile Asn Leu Asn Leu
325 330 335

Val Ala Ile Gly Lys Glu Ile Val Lys Lys Cys Gly Gly Val Pro Leu
340 345 350

Ala Ala Lys Thr Leu Gly Gly Ile Leu Arg Phe Lys Arg Glu Glu Arg
355 360 365

Gln Trp Glu His Val Arg Asp Ser Glu Ile Trp Lys Leu Pro Gln Glu
370 375 380

Glu Ser Ser Ile Leu Pro Ala Leu Arg Leu Ser Tyr His His Leu Pro
385 390 395 400

Leu Asp Leu Arg Gln Cys Phe Thr Tyr Cys Ala Val Phe Pro Lys Asp
405 410 415

Thr Glu Met Glu Lys Gly Asn Leu Ile Ser Leu Trp Met Ala His Gly
420 425 430

Phe Ile Leu Ser Lys Gly Asn Leu Glu Leu Glu Asn Val Gly Asn Glu
435 440 445

Val Trp Asn Glu Leu Tyr Leu Arg Ser Phe Phe Gln Glu Ile Glu Val
450 455 460

Lys Ser Gly Gln Thr Tyr Phe Lys Met His Asp Leu Ile His Asp Leu
465 470 475 480

Ala Thr Ser Leu Phe Ser Ala Ser Thr Ser Ser Ser Asn Ile Arg Glu
485 490 495

Ile Ile Val Glu Asn Tyr Ile His Met Met Ser Ile Gly Phe Thr Lys
500 505 510

Val Val Ser Ser Tyr Ser Leu Ser His Leu Gln Lys Phe Val Ser Leu
515 520 525

Arg Val Leu Asn Leu Ser Asp Ile Lys Leu Lys Gln Leu Pro Ser Ser
530 535 540

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Ile Gly Asp Leu Val His Leu Arg Tyr Leu Asn Leu Ser Gly Asn Thr
545                 550                 555                 560

Ser Ile Arg Ser Leu Pro Asn Gln Leu Cys Lys Leu Gln Asn Leu Gln
                565                 570                 575

Thr Leu Asp Leu His Gly Cys His Ser Leu Cys Cys Leu Pro Lys Glu
            580                 585                 590

Thr Ser Lys Leu Gly Ser Leu Arg Asn Leu Leu Leu Asp Gly Cys Tyr
        595                 600                 605

Gly Leu Thr Cys Met Pro Pro Arg Ile Gly Ser Leu Thr Cys Leu Lys
    610                 615                 620

Thr Leu Ser Arg Phe Val Val Gly Ile Gln Lys Lys Ser Cys Gln Leu
625                 630                 635                 640

Gly Glu Leu Arg Asn Leu Asn Leu Tyr Gly Ser Ile Glu Ile Thr His
                645                 650                 655

Leu Glu Arg Val Lys Asn Asp Met Asp Ala Lys Glu Ala Asn Leu Ser
            660                 665                 670

Ala Lys Glu Asn Leu His Ser Leu Ser Met Lys Trp Asp Asp Asp Glu
        675                 680                 685

Arg Pro Arg Ile Tyr Glu Ser Glu Lys Val Glu Val Leu Glu Ala Leu
    690                 695                 700

Lys Pro His Ser Asn Leu Thr Cys Leu Thr Ile Arg Gly Phe Arg Gly
705                 710                 715                 720

Ile Arg Leu Pro Asp Trp Met Asn His Ser Val Leu Lys Asn Val Val
                725                 730                 735

Ser Ile Glu Ile Ile Ser Cys Lys Asn Cys Ser Cys Leu Pro Pro Phe
            740                 745                 750

Gly Glu Leu Pro Cys Leu Lys Ser Leu Glu Leu Trp Arg Gly Ser Ala
        755                 760                 765

Glu Val Glu Tyr Val Asp Ser Gly Phe Pro Thr Arg Arg Arg Phe Pro
    770                 775                 780
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Ser Leu Arg Lys Leu Asn Ile Arg Glu Phe Gly Asn Leu Lys Gly Leu
785                 790                 795                 800

Leu Lys Lys Glu Gly Glu Glu Gln Cys Pro Val Leu Glu Glu Ile Glu
                805                 810                 815

Ile Lys Cys Cys Pro Met Phe Val Ile Pro Thr Leu Ser Ser Val Lys
            820                 825                 830

Lys Leu Val Val Ser Gly Asp Lys Ser Asp Ala Ile Gly Phe Ser Ser
        835                 840                 845

Ile Ser Asn Leu Met Ala Leu Thr Ser Leu Gln Ile Arg Tyr Asn Lys
    850                 855                 860

Glu Asp Ala Ser Leu Pro Glu Glu Met Phe Lys Ser Leu Ala Asn Leu
865                 870                 875                 880

Lys Tyr Leu Asn Ile Ser Phe Tyr Phe Asn Leu Lys Glu Leu Pro Thr
                885                 890                 895

Ser Leu Ala Ser Leu Asn Ala Leu Lys His Leu Glu Ile His Ser Cys
            900                 905                 910

Tyr Ala Leu Glu Ser Leu Pro Glu Glu Gly Val Lys Gly Leu Ile Ser
        915                 920                 925

Leu Thr Gln Leu Ser Ile Thr Tyr Cys Glu Met Leu Gln Cys Leu Pro
    930                 935                 940

Glu Gly Leu Gln His Leu Thr Ala Leu Thr Asn Leu Ser Val Glu Phe
945                 950                 955                 960

Cys Pro Thr Leu Ala Lys Arg Cys Glu Lys Gly Ile Gly Glu Asp Trp
                965                 970                 975

Tyr Lys Ile Ala His Ile Pro Arg Val Phe Ile Tyr
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Met
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Ala Glu Ala Phe Leu Gln Val Leu Leu Asp Asn Leu Thr Cys Phe Ile
5 10 15

caa ggg gaa ctt gga ttg att ctt ggt ttt aag gat gag ttc gaa aag 155
Gln Gly Glu Leu Gly Leu Ile Leu Gly Phe Lys Asp Glu Phe Glu Lys
20 25 30

ctt caa agc acg ttt act aca atc caa gct gtg cta gaa gat gct cag 203
Leu Gln Ser Thr Phe Thr Thr Ile Gln Ala Val Leu Glu Asp Ala Gln
35 40 45

aag aag caa ttg aag gac aag gca ata gaa aat tgg ttg cag aaa ctc 251
Lys Lys Gln Leu Lys Asp Lys Ala Ile Glu Asn Trp Leu Gln Lys Leu
50 55 60 65

aat gct gct gca tat gag gct gat gac atc ttg gac gaa tgt aaa act 299
Asn Ala Ala Ala Tyr Glu Ala Asp Asp Ile Leu Asp Glu Cys Lys Thr
70 75 80

gag gca cca att aga cag aag aag aac aaa tat ggg tgt tat cat cca 347
Glu Ala Pro Ile Arg Gln Lys Lys Asn Lys Tyr Gly Cys Tyr His Pro
85 90 95

aac gtt atc act ttt cgt cac aag att ggg aaa agg atg aaa aag att 395
Asn Val Ile Thr Phe Arg His Lys Ile Gly Lys Arg Met Lys Lys Ile
100 105 110

atg gag aaa cta gat gta att gca gcg gaa cga att aag ttt cat ttg 443
Met Glu Lys Leu Asp Val Ile Ala Ala Glu Arg Ile Lys Phe His Leu
115 120 125

gat gaa agg act ata gag aga caa gtt gct aca cgc caa aca gg 487
Asp Glu Arg Thr Ile Glu Arg Gln Val Ala Thr Arg Gln Thr Gly
130 135 140

tgctcatctt agatattttt ctgaaaaaac agctttatat catcaaattc atgtgtgttt 547

tgggaattcg tctaatctaa atgttcgtct caagtctaag tagataagtg gatccagctt 607

tggatttatt aatctattag ctaaatctgt ttagtgaagt ttttaacata tataacctca 667

gataaatcca tagcttactc ataggattag gataggcccc caagtctaaa tgacaggata 727

aagccagagt tgttttagct cttataaatt aacaatgata ataatgtgaa ttcaaaaaag 787

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tgcatttttt taatttgaaa tatttctgct gcttctcaag cttatcattg tctttttact    847

gtgcaaaatt ctactttgta tttttgctga ctcctaccga gcttgggcca gg t ttt      903
                                                            Phe
                                                            145

gtt ttg aat gaa cca caa gtt tat gga aga gac aaa gaa aag gac gag      951
Val Leu Asn Glu Pro Gln Val Tyr Gly Arg Asp Lys Glu Lys Asp Glu
                150                 155                 160

ata gtg aaa atc ctg ata aac aat gtt agc aat gcc caa aca ctt cca      999
Ile Val Lys Ile Leu Ile Asn Asn Val Ser Asn Ala Gln Thr Leu Pro
            165                 170                 175

gtc ctc cca ata ctt ggt atg ggg gga cta gga aag acg act ctt gcc     1047
Val Leu Pro Ile Leu Gly Met Gly Gly Leu Gly Lys Thr Thr Leu Ala
        180                 185                 190

caa atg gtc ttc aat gat cag aga gta att gag cat ttc cat ccc aaa     1095
Gln Met Val Phe Asn Asp Gln Arg Val Ile Glu His Phe His Pro Lys
    195                 200                 205

ata tgg att tgt gtc tcg gaa gat ttt aat gag aag agg ttg ata aag     1143
Ile Trp Ile Cys Val Ser Glu Asp Phe Asn Glu Lys Arg Leu Ile Lys
210                 215                 220                 225

gaa att gta gaa tct att gaa gaa aag tca ctt ggt ggc atg gac ttg     1191
Glu Ile Val Glu Ser Ile Glu Glu Lys Ser Leu Gly Gly Met Asp Leu
                230                 235                 240

gct cca ctt caa aag aag ctt cgg gac ttg ctg aat gga aaa aaa tat     1239
Ala Pro Leu Gln Lys Lys Leu Arg Asp Leu Leu Asn Gly Lys Lys Tyr
            245                 250                 255

ttg ctc gtc tta gat gat gtt tgg aat gaa gat caa gat aag tgg gct     1287
Leu Leu Val Leu Asp Asp Val Trp Asn Glu Asp Gln Asp Lys Trp Ala
        260                 265                 270

aag tta aga caa gtc ttg aag gtt gga gca agt ggc gct tct gtt cta     1335
Lys Leu Arg Gln Val Leu Lys Val Gly Ala Ser Gly Ala Ser Val Leu
    275                 280                 285

acc act act cgt ctt gaa aag gtt gga tca att atg gga aca ttg caa     1383
Thr Thr Thr Arg Leu Glu Lys Val Gly Ser Ile Met Gly Thr Leu Gln
290                 295                 300                 305

cca tat gaa ttg tca aat ttg tct caa gaa gat tgt tgg ttg ttg ttc     1431
Pro Tyr Glu Leu Ser Asn Leu Ser Gln Glu Asp Cys Trp Leu Leu Phe
                310                 315                 320

atg caa cgt gca ttt ggg cac caa gaa gaa ata aat ctt aat ctt gtg     1479
Met Gln Arg Ala Phe Gly His Gln Glu Glu Ile Asn Leu Asn Leu Val
            325                 330                 335

gct atc gga aag gag att gtg aaa aaa tgt ggt ggt gtg cct cta gca     1527
Ala Ile Gly Lys Glu Ile Val Lys Lys Cys Gly Gly Val Pro Leu Ala
        340                 345                 350

gct aaa act ctt gga ggt att ttg cgc ttt aag aga gaa gaa aga cag     1575
Ala Lys Thr Leu Gly Gly Ile Leu Arg Phe Lys Arg Glu Glu Arg Gln
    355                 360                 365
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tgg gaa cat gtg aga gat agt gag att tgg aaa ttg cct caa gaa gaa     1623
Trp Glu His Val Arg Asp Ser Glu Ile Trp Lys Leu Pro Gln Glu Glu
370                 375                 380                 385

agt tct att ctg cct gcc ctg aga ctt agt tac cat cac ctt cca ctt     1671
Ser Ser Ile Leu Pro Ala Leu Arg Leu Ser Tyr His His Leu Pro Leu
                390                 395                 400

gat ttg aga caa tgc ttt aca tat tgt gca gta ttc cca aag gat acc     1719
Asp Leu Arg Gln Cys Phe Thr Tyr Cys Ala Val Phe Pro Lys Asp Thr
            405                 410                 415

gaa atg gaa aag gga aat cta atc tct ctc tgg atg gca cat ggt ttt     1767
Glu Met Glu Lys Gly Asn Leu Ile Ser Leu Trp Met Ala His Gly Phe
        420                 425                 430

att tta tcg aaa gga aac ttg gag cta gag aat gta ggt aat gaa gta     1815
Ile Leu Ser Lys Gly Asn Leu Glu Leu Glu Asn Val Gly Asn Glu Val
    435                 440                 445

tgg aat gaa tta tac ttg agg tct ttc ttc caa gag att gaa gtt aaa     1863
Trp Asn Glu Leu Tyr Leu Arg Ser Phe Phe Gln Glu Ile Glu Val Lys
450                 455                 460                 465

tct ggt caa act tat ttc aag atg cat gat ctc att cat gat ctg gca     1911
Ser Gly Gln Thr Tyr Phe Lys Met His Asp Leu Ile His Asp Leu Ala
                470                 475                 480

aca tct cta ttt tcg gca agc aca tca agc agc aat atc cga gaa ata     1959
Thr Ser Leu Phe Ser Ala Ser Thr Ser Ser Ser Asn Ile Arg Glu Ile
            485                 490                 495

att gta gaa aat tac ata cat atg atg tcc att ggt ttc act aaa gtg     2007
Ile Val Glu Asn Tyr Ile His Met Met Ser Ile Gly Phe Thr Lys Val
        500                 505                 510

gta tct tct tac tct ctt tcc cac ttg cag aag ttt gtc tcg ttg agg     2055
Val Ser Ser Tyr Ser Leu Ser His Leu Gln Lys Phe Val Ser Leu Arg
    515                 520                 525

gtg ctt aat cta agt gac ata aaa ctt aag cag tta ccg tct tcc att     2103
Val Leu Asn Leu Ser Asp Ile Lys Leu Lys Gln Leu Pro Ser Ser Ile
530                 535                 540                 545

gga gat cta gta cat tta aga tac cta aac ttg tct ggc aat act agt     2151
Gly Asp Leu Val His Leu Arg Tyr Leu Asn Leu Ser Gly Asn Thr Ser
                550                 555                 560

att cgt agt ctt cca aac cag tta tgc aag ctt caa aat ctg cag act     2199
Ile Arg Ser Leu Pro Asn Gln Leu Cys Lys Leu Gln Asn Leu Gln Thr
            565                 570                 575

ctt gat cta cat ggc tgt cat tca ctt tgt tgt ttg cca aaa gaa aca     2247
Leu Asp Leu His Gly Cys His Ser Leu Cys Cys Leu Pro Lys Glu Thr
        580                 585                 590

agc aaa ctt ggt agt ctt cga aat ctt tta ctt gat ggt tgc tat gga     2295
Ser Lys Leu Gly Ser Leu Arg Asn Leu Leu Leu Asp Gly Cys Tyr Gly
    595                 600                 605
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ttg act tgt atg cca cca agg ata gga tct ttg aca tgc ctt aag act     2343
Leu Thr Cys Met Pro Pro Arg Ile Gly Ser Leu Thr Cys Leu Lys Thr
610                 615                 620                 625

cta agt aga ttt gtg gtg gga att cag aag aaa agt tgt caa ctt ggt     2391
Leu Ser Arg Phe Val Val Gly Ile Gln Lys Lys Ser Cys Gln Leu Gly
                630                 635                 640

gaa tta cga aac ctg aat ctc tat ggc tca att gaa atc acg cat ctt     2439
Glu Leu Arg Asn Leu Asn Leu Tyr Gly Ser Ile Glu Ile Thr His Leu
            645                 650                 655

gag aga gtg aag aat gat atg gat gca aaa gaa gcc aat tta tct gca     2487
Glu Arg Val Lys Asn Asp Met Asp Ala Lys Glu Ala Asn Leu Ser Ala
        660                 665                 670

aaa gaa aat ctg cat tct tta agc atg aaa tgg gat gac gat gaa cgt     2535
Lys Glu Asn Leu His Ser Leu Ser Met Lys Trp Asp Asp Asp Glu Arg
    675                 680                 685

cca cgt ata tat gaa tca gaa aaa gtt gaa gtg ctt gaa gct ctc aaa     2583
Pro Arg Ile Tyr Glu Ser Glu Lys Val Glu Val Leu Glu Ala Leu Lys
690                 695                 700                 705

cca cac tcc aat ctg act tgt tta aca atc agg ggc ttc aga gga atc     2631
Pro His Ser Asn Leu Thr Cys Leu Thr Ile Arg Gly Phe Arg Gly Ile
                710                 715                 720

cgt ctc cca gac tgg atg aat cac tca gtt ttg aaa aat gtt gtc tct     2679
Arg Leu Pro Asp Trp Met Asn His Ser Val Leu Lys Asn Val Val Ser
            725                 730                 735

att gaa atc atc agt tgc aaa aac tgc tca tgc tta cca ccc ttt ggt     2727
Ile Glu Ile Ile Ser Cys Lys Asn Cys Ser Cys Leu Pro Pro Phe Gly
        740                 745                 750

gag ctg cct tgt cta aaa agt cta gag tta tgg agg ggg tct gcg gaa     2775
Glu Leu Pro Cys Leu Lys Ser Leu Glu Leu Trp Arg Gly Ser Ala Glu
    755                 760                 765

gtg gag tat gtt gat tct gga ttc cct aca aga aga agg ttt cca tct     2823
Val Glu Tyr Val Asp Ser Gly Phe Pro Thr Arg Arg Arg Phe Pro Ser
770                 775                 780                 785

ctg aga aaa ctt aat ata cgc gaa ttt gat aat ctg aaa gga ttg ctg     2871
Leu Arg Lys Leu Asn Ile Arg Glu Phe Asp Asn Leu Lys Gly Leu Leu
                790                 795                 800

aaa aag gaa gga gaa gag caa tgc cct gtg ctt gaa gag ata gag att     2919
Lys Lys Glu Gly Glu Glu Gln Cys Pro Val Leu Glu Glu Ile Glu Ile
            805                 810                 815

aaa tgt tgc cct atg ttt gtt att cca acc ctt tct tct gtc aag aaa     2967
Lys Cys Cys Pro Met Phe Val Ile Pro Thr Leu Ser Ser Val Lys Lys
        820                 825                 830

ttg gta gtt agt ggg gac aag tca gat gca ata ggt ttc agt tcc ata     3015
Leu Val Val Ser Gly Asp Lys Ser Asp Ala Ile Gly Phe Ser Ser Ile
    835                 840                 845

tct aat ctc atg gct ctt act tcc ctc caa att cgc tat aac aaa gaa     3063
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Ser Asn Leu Met Ala Leu Thr Ser Leu Gln Ile Arg Tyr Asn Lys Glu
850                 855                 860                 865

gat gct tca ctc cca gaa gag atg ttc aaa agc ctt gca aat ctc aaa     3111
Asp Ala Ser Leu Pro Glu Glu Met Phe Lys Ser Leu Ala Asn Leu Lys
                870                 875                 880

tac ttg aat atc tct ttt tac ttc aat ctt aaa gag ctg cct acc agc     3159
Tyr Leu Asn Ile Ser Phe Tyr Phe Asn Leu Lys Glu Leu Pro Thr Ser
            885                 890                 895

ctg gct agt ctc aat gct ttg aag cat ctg gaa att cat agt tgt tat     3207
Leu Ala Ser Leu Asn Ala Leu Lys His Leu Glu Ile His Ser Cys Tyr
        900                 905                 910

gca cta gag agt ctc ccc gag gaa ggt gtg aaa ggt tta att tca ctc     3255
Ala Leu Glu Ser Leu Pro Glu Glu Gly Val Lys Gly Leu Ile Ser Leu
    915                 920                 925

aca cag tta tcc ata aca tac tgt gaa atg cta caa tgt tta ccg gag     3303
Thr Gln Leu Ser Ile Thr Tyr Cys Glu Met Leu Gln Cys Leu Pro Glu
930                 935                 940                 945

gga ttg cag cac cta aca gcc ctc aca aat tta tca gtt gag ttt tgt     3351
Gly Leu Gln His Leu Thr Ala Leu Thr Asn Leu Ser Val Glu Phe Cys
                950                 955                 960

cca aca ctg gcc aag cgg tgt gag aag gga ata gga gaa gac tgg tac     3399
Pro Thr Leu Ala Lys Arg Cys Glu Lys Gly Ile Gly Glu Asp Trp Tyr
            965                 970                 975

aaa att gct cac att cct cgt gtg ttt att tat tagtattccc aattagatgt   3452
Lys Ile Ala His Ile Pro Arg Val Phe Ile Tyr
        980                 985

aattttctga ttttcttttg gaaacaaatc aactatttgt aagatctatt tgtattatac   3512

ttgatttttc ttgggtctgt aacaataaat atttgaaatt tttcatatta agattcagaa   3572

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Ile Gln Gly Glu Leu Gly Leu Ile Leu Gly Phe Lys Asp Glu Phe Glu
            20                  25                  30

Lys Leu Gln Ser Thr Phe Thr Thr Ile Gln Ala Val Leu Glu Asp Ala
        35                  40                  45
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Gln Lys Lys Gln Leu Lys Asp Lys Ala Ile Glu Asn Trp Leu Gln Lys
    50                  55                  60

Leu Asn Ala Ala Ala Tyr Glu Ala Asp Asp Ile Leu Asp Glu Cys Lys
65                  70                  75                  80

Thr Glu Ala Pro Ile Arg Gln Lys Lys Asn Lys Tyr Gly Cys Tyr His
                85                  90                  95

Pro Asn Val Ile Thr Phe Arg His Lys Ile Gly Lys Arg Met Lys Lys
            100                 105                 110

Ile Met Glu Lys Leu Asp Val Ile Ala Ala Glu Arg Ile Lys Phe His
        115                 120                 125

Leu Asp Glu Arg Thr Ile Glu Arg Gln Val Ala Thr Arg Gln Thr Gly
    130                 135                 140

Phe Val Leu Asn Glu Pro Gln Val Tyr Gly Arg Asp Lys Glu Lys Asp
145                 150                 155                 160

Glu Ile Val Lys Ile Leu Ile Asn Asn Val Ser Asn Ala Gln Thr Leu
                165                 170                 175

Pro Val Leu Pro Ile Leu Gly Met Gly Gly Leu Gly Lys Thr Thr Leu
            180                 185                 190

Ala Gln Met Val Phe Asn Asp Gln Arg Val Ile Glu His Phe His Pro
        195                 200                 205

Lys Ile Trp Ile Cys Val Ser Glu Asp Phe Asn Glu Lys Arg Leu Ile
    210                 215                 220

Lys Glu Ile Val Glu Ser Ile Glu Glu Lys Ser Leu Gly Gly Met Asp
225                 230                 235                 240

Leu Ala Pro Leu Gln Lys Lys Leu Arg Asp Leu Leu Asn Gly Lys Lys
                245                 250                 255

Tyr Leu Leu Val Leu Asp Asp Val Trp Asn Glu Asp Gln Asp Lys Trp
            260                 265                 270

Ala Lys Leu Arg Gln Val Leu Lys Val Gly Ala Ser Gly Ala Ser Val
        275                 280                 285

Leu Thr Thr Thr Arg Leu Glu Lys Val Gly Ser Ile Met Gly Thr Leu
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290 295 300

Gln Pro Tyr Glu Leu Ser Asn Leu Ser Gln Glu Asp Cys Trp Leu Leu
305 310 315 320

Phe Met Gln Arg Ala Phe Gly His Gln Glu Glu Ile Asn Leu Asn Leu
325 330 335

Val Ala Ile Gly Lys Glu Ile Val Lys Lys Cys Gly Gly Val Pro Leu
340 345 350

Ala Ala Lys Thr Leu Gly Gly Ile Leu Arg Phe Lys Arg Glu Glu Arg
355 360 365

Gln Trp Glu His Val Arg Asp Ser Glu Ile Trp Lys Leu Pro Gln Glu
370 375 380

Glu Ser Ser Ile Leu Pro Ala Leu Arg Leu Ser Tyr His His Leu Pro
385 390 395 400

Leu Asp Leu Arg Gln Cys Phe Thr Tyr Cys Ala Val Phe Pro Lys Asp
405 410 415

Thr Glu Met Glu Lys Gly Asn Leu Ile Ser Leu Trp Met Ala His Gly
420 425 430

Phe Ile Leu Ser Lys Gly Asn Leu Glu Leu Glu Asn Val Gly Asn Glu
435 440 445

Val Trp Asn Glu Leu Tyr Leu Arg Ser Phe Phe Gln Glu Ile Glu Val
450 455 460

Lys Ser Gly Gln Thr Tyr Phe Lys Met His Asp Leu Ile His Asp Leu
465 470 475 480

Ala Thr Ser Leu Phe Ser Ala Ser Thr Ser Ser Ser Asn Ile Arg Glu
485 490 495

Ile Ile Val Glu Asn Tyr Ile His Met Met Ser Ile Gly Phe Thr Lys
500 505 510

Val Val Ser Ser Tyr Ser Leu Ser His Leu Gln Lys Phe Val Ser Leu
515 520 525

Arg Val Leu Asn Leu Ser Asp Ile Lys Leu Lys Gln Leu Pro Ser Ser
530 535 540

Ile Gly Asp Leu Val His Leu Arg Tyr Leu Asn Leu Ser Gly Asn Thr
545 550 555 560

Ser Ile Arg Ser Leu Pro Asn Gln Leu Cys Lys Leu Gln Asn Leu Gln
565 570 575

Thr Leu Asp Leu His Gly Cys His Ser Leu Cys Cys Leu Pro Lys Glu
580 585 590

Thr Ser Lys Leu Gly Ser Leu Arg Asn Leu Leu Leu Asp Gly Cys Tyr
595 600 605

Gly Leu Thr Cys Met Pro Pro Arg Ile Gly Ser Leu Thr Cys Leu Lys
610 615 620

Thr Leu Ser Arg Phe Val Val Gly Ile Gln Lys Lys Ser Cys Gln Leu
625 630 635 640

Gly Glu Leu Arg Asn Leu Asn Leu Tyr Gly Ser Ile Glu Ile Thr His
645 650 655

Leu Glu Arg Val Lys Asn Asp Met Asp Ala Lys Glu Ala Asn Leu Ser
660 665 670

Ala Lys Glu Asn Leu His Ser Leu Ser Met Lys Trp Asp Asp Asp Glu
675 680 685

Arg Pro Arg Ile Tyr Glu Ser Glu Lys Val Glu Val Leu Glu Ala Leu
690 695 700

Lys Pro His Ser Asn Leu Thr Cys Leu Thr Ile Arg Gly Phe Arg Gly
705 710 715 720

Ile Arg Leu Pro Asp Trp Met Asn His Ser Val Leu Lys Asn Val Val
725 730 735

Ser Ile Glu Ile Ile Ser Cys Lys Asn Cys Ser Cys Leu Pro Pro Phe
740 745 750

Gly Glu Leu Pro Cys Leu Lys Ser Leu Glu Leu Trp Arg Gly Ser Ala
755 760 765

Glu Val Glu Tyr Val Asp Ser Gly Phe Pro Thr Arg Arg Arg Phe Pro
770 775 780

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Ser Leu Arg Lys Leu Asn Ile Arg Glu Phe Asp Asn Leu Lys Gly Leu
785                 790                 795                 800

Leu Lys Lys Glu Gly Glu Glu Gln Cys Pro Val Leu Glu Glu Ile Glu
                805                 810                 815

Ile Lys Cys Cys Pro Met Phe Val Ile Pro Thr Leu Ser Ser Val Lys
            820                 825                 830

Lys Leu Val Val Ser Gly Asp Lys Ser Asp Ala Ile Gly Phe Ser Ser
        835                 840                 845

Ile Ser Asn Leu Met Ala Leu Thr Ser Leu Gln Ile Arg Tyr Asn Lys
    850                 855                 860

Glu Asp Ala Ser Leu Pro Glu Glu Met Phe Lys Ser Leu Ala Asn Leu
865                 870                 875                 880

Lys Tyr Leu Asn Ile Ser Phe Tyr Phe Asn Leu Lys Glu Leu Pro Thr
                885                 890                 895

Ser Leu Ala Ser Leu Asn Ala Leu Lys His Leu Glu Ile His Ser Cys
            900                 905                 910

Tyr Ala Leu Glu Ser Leu Pro Glu Glu Gly Val Lys Gly Leu Ile Ser
        915                 920                 925

Leu Thr Gln Leu Ser Ile Thr Tyr Cys Glu Met Leu Gln Cys Leu Pro
    930                 935                 940

Glu Gly Leu Gln His Leu Thr Ala Leu Thr Asn Leu Ser Val Glu Phe
945                 950                 955                 960

Cys Pro Thr Leu Ala Lys Arg Cys Glu Lys Gly Ile Gly Glu Asp Trp
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Tyr Lys Ile Ala His Ile Pro Arg Val Phe Ile Tyr
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Ala Glu Ala Phe Leu Gln Val Leu Leu Asp Asn Leu Thr Cys Phe Ile
5 10 15

caa ggg gaa gtt gga ttg att ctt ggt ttt aag gat gag ttc gaa aag 155
Gln Gly Glu Val Gly Leu Ile Leu Gly Phe Lys Asp Glu Phe Glu Lys
20 25 30

ctt caa agc aca ttt act aca atc caa gct gtg cta gaa gat gct cag 203
Leu Gln Ser Thr Phe Thr Thr Ile Gln Ala Val Leu Glu Asp Ala Gln
35 40 45

aag aag caa ttg aag gac aag gca ata gaa aat tgg ttg cag aaa ctc 251
Lys Lys Gln Leu Lys Asp Lys Ala Ile Glu Asn Trp Leu Gln Lys Leu
50 55 60 65

aat gct gct gta tat gaa gct gac gac atc ttg gac gaa tgt aaa act 299
Asn Ala Ala Val Tyr Glu Ala Asp Asp Ile Leu Asp Glu Cys Lys Thr
70 75 80

gag gca cca att aga cag aag aag aac aaa tat ggg tgt tat cat cca 347
Glu Ala Pro Ile Arg Gln Lys Lys Asn Lys Tyr Gly Cys Tyr His Pro
85 90 95

aac gtt atc gct ttc cgt cac aag att ggg aaa agg atg aaa aag att 395
Asn Val Ile Ala Phe Arg His Lys Ile Gly Lys Arg Met Lys Lys Ile
100 105 110

atg gag aaa cta gat gta att gca gcg gaa cga att aag ttt cat ttg 443
Met Glu Lys Leu Asp Val Ile Ala Ala Glu Arg Ile Lys Phe His Leu
115 120 125

gct gaa agg act aca gag aga caa gtt gct aca cgc caa aca ggt gct 491
Ala Glu Arg Thr Thr Glu Arg Gln Val Ala Thr Arg Gln Thr Gly Ala
130 135 140 145

cat ctt aga tat ttt tct aaaaaaacag ctttatatca tgaaattcat 539
His Leu Arg Tyr Phe Ser
150

gtgtgtttgg gatttttttct aatctaaatg ttgtctcaag tctaagtaga taagtggatc 599

cagatttgga tatattaata tattatctaa atttgtttcg tgaaattttt aacagataaa 659

gcctgagttg ttttagacat tataaattaa caatgataat aatgtgaatt caaaaaagtg 719

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cattatgtct gctgcttctc aagcttatca ttgtctcttt attgtgcaaa attcttcttc    779

gttttttttg ctg act cct act gag ctt gga cca ggt ttt gtt tta aat gaa    830
           Leu Thr Pro Thr Glu Leu Gly Pro Gly Phe Val Leu Asn Glu
                       155                 160                 165

cca caa gtt tat gga aga gac aaa gaa aag gat gag ata gtg aaa atc      878
Pro Gln Val Tyr Gly Arg Asp Lys Glu Lys Asp Glu Ile Val Lys Ile
                   170                 175                 180

ctg ata aac att gtt agc gat gcc caa aca ctt tca gtc ctc cca ata      926
Leu Ile Asn Ile Val Ser Asp Ala Gln Thr Leu Ser Val Leu Pro Ile
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ctt ggt atg ggg gga tta gga aag acg aca ctt gcc caa atg gtc ttc      974
Leu Gly Met Gly Gly Leu Gly Lys Thr Thr Leu Ala Gln Met Val Phe
           200                 205                 210

aat gat cag aga gta att gag cat ttc ctt ccc aaa ata tgg att tgt     1022
Asn Asp Gln Arg Val Ile Glu His Phe Leu Pro Lys Ile Trp Ile Cys
       215                 220                 225

gtc tcg gaa gat ttt aat gag aag agg ttg ata aag gaa att gta gaa     1070
Val Ser Glu Asp Phe Asn Glu Lys Arg Leu Ile Lys Glu Ile Val Glu
   230                 235                 240                 245

tct att gaa gaa aag tca ctt ggt gac atg gac ttg gct cca ctt caa     1118
Ser Ile Glu Glu Lys Ser Leu Gly Asp Met Asp Leu Ala Pro Leu Gln
               250                 255                 260

aag aag ctt cag gac ttg ctg aat gga aaa aaa tat ttg ctt gtc tta     1166
Lys Lys Leu Gln Asp Leu Leu Asn Gly Lys Lys Tyr Leu Leu Val Leu
           265                 270                 275

gat gat att tgg aat gaa gat caa gat aag tgg gct aag tta cga gaa     1214
Asp Asp Ile Trp Asn Glu Asp Gln Asp Lys Trp Ala Lys Leu Arg Glu
       280                 285                 290

gtg ttg aag gtt gga gca agt ggt gct tct atc cta acc act act cgt     1262
Val Leu Lys Val Gly Ala Ser Gly Ala Ser Ile Leu Thr Thr Thr Arg
   295                 300                 305

ctt gaa aag gtt gga tca att atg caa act ttg caa cca tat gaa ttg     1310
Leu Glu Lys Val Gly Ser Ile Met Gln Thr Leu Gln Pro Tyr Glu Leu
310                 315                 320                 325

tca aac ttg tgt caa gaa gat tgc tgg ttg ttg ttc atg caa cgt gca     1358
Ser Asn Leu Cys Gln Glu Asp Cys Trp Leu Leu Phe Met Gln Arg Ala
               330                 335                 340

ttt ggg cac caa gaa gaa ata aat cat aat ctt gtg gct atc gga aag     1406
Phe Gly His Gln Glu Glu Ile Asn His Asn Leu Val Ala Ile Gly Lys
           345                 350                 355

gag ata gtg aaa aaa tgt ggt ggt gtg cct cta gca gct aaa act ctt     1454
Glu Ile Val Lys Lys Cys Gly Gly Val Pro Leu Ala Ala Lys Thr Leu
       360                 365                 370

gga ggt att ttg cga ttc aag aga caa gaa aga cag tgg gaa cat gtg     1502
Gly Gly Ile Leu Arg Phe Lys Arg Gln Glu Arg Gln Trp Glu His Val
   375                 380                 385
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aga gat agt gag att tgg aaa ttg cct caa gaa gaa agt tct att ctg     1550
Arg Asp Ser Glu Ile Trp Lys Leu Pro Gln Glu Glu Ser Ser Ile Leu
390                 395                 400                 405

ccg gcc ctg aaa ctt agt tac cat cat ctt cca ctt gat ttg aga caa     1598
Pro Ala Leu Lys Leu Ser Tyr His His Leu Pro Leu Asp Leu Arg Gln
                410                 415                 420

tgc ttt tca tat tgt gca gta ttc cca aag gat acc aaa atg gaa aag     1646
Cys Phe Ser Tyr Cys Ala Val Phe Pro Lys Asp Thr Lys Met Glu Lys
            425                 430                 435

gaa aat cta atc tct ctc tgg atg gca cat ggt ttt ctt tta tcg aaa     1694
Glu Asn Leu Ile Ser Leu Trp Met Ala His Gly Phe Leu Leu Ser Lys
        440                 445                 450

gga aac ttg gag cta gag gat gta ggt aat gaa gta tgg aat gaa tta     1742
Gly Asn Leu Glu Leu Glu Asp Val Gly Asn Glu Val Trp Asn Glu Leu
    455                 460                 465

tac ttg agg tct ttc ttc caa gag att gaa gtt aca tat ggt aaa act     1790
Tyr Leu Arg Ser Phe Phe Gln Glu Ile Glu Val Thr Tyr Gly Lys Thr
470                 475                 480                 485

tat ttc aag atg cat gat ctc atc cat gat ttg gct aca tct cta ttt     1838
Tyr Phe Lys Met His Asp Leu Ile His Asp Leu Ala Thr Ser Leu Phe
                490                 495                 500

tcg gca agc gca tca agc aac aat atc cgt gaa ata aat gta aaa ggt     1886
Ser Ala Ser Ala Ser Ser Asn Asn Ile Arg Glu Ile Asn Val Lys Gly
            505                 510                 515

tac cca cat atg atg tcg att ggc ttt gca aaa gtg gtg tct ttt tac     1934
Tyr Pro His Met Met Ser Ile Gly Phe Ala Lys Val Val Ser Phe Tyr
        520                 525                 530

tct cgt tct cac ttc caa aag ttt gtc tcg tta agg gtg ctt aat cta     1982
Ser Arg Ser His Phe Gln Lys Phe Val Ser Leu Arg Val Leu Asn Leu
    535                 540                 545

agt aac tta gaa ctc aag cag tta cca tct tca att ggg gat cta gta     2030
Ser Asn Leu Glu Leu Lys Gln Leu Pro Ser Ser Ile Gly Asp Leu Val
550                 555                 560                 565

cat tta aga tac cta aac ttg tct gac aat aat aga att cgt agt ctt     2078
His Leu Arg Tyr Leu Asn Leu Ser Asp Asn Asn Arg Ile Arg Ser Leu
                570                 575                 580

ccc aag cag tta tgc aag ctt caa aat ctg cag act ctt gat cta cgt     2126
Pro Lys Gln Leu Cys Lys Leu Gln Asn Leu Gln Thr Leu Asp Leu Arg
            585                 590                 595

tgt tgc tac aga ctt tct tgt ttg cca aaa gaa aca agc aaa ctt ggt     2174
Cys Cys Tyr Arg Leu Ser Cys Leu Pro Lys Glu Thr Ser Lys Leu Gly
        600                 605                 610

agt ctc cga aat ctt tta ctt gat cgt tgc cat gga ttg act tgt atg     2222
Ser Leu Arg Asn Leu Leu Leu Asp Arg Cys His Gly Leu Thr Cys Met
    615                 620                 625
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cca cca agg ata gga tca ttg aca tgc ctt aag act cta gat cgc ttt      2270
Pro Pro Arg Ile Gly Ser Leu Thr Cys Leu Lys Thr Leu Asp Arg Phe
630                 635                 640                 645

gca atg gga agg gag aaa agt cct caa att ggt gaa tta cga aac ctg      2318
Ala Met Gly Arg Glu Lys Ser Pro Gln Ile Gly Glu Leu Arg Asn Leu
                650                 655                 660

aat ctc tat ggc tca att tca atc acg cat ctt gag aga gtg aag aat      2366
Asn Leu Tyr Gly Ser Ile Ser Ile Thr His Leu Glu Arg Val Lys Asn
            665                 670                 675

gat atg gat gca aaa gaa gcc aat tta tct tca aaa gaa aat ctg cat      2414
Asp Met Asp Ala Lys Glu Ala Asn Leu Ser Ser Lys Glu Asn Leu His
        680                 685                 690

tct tta agt atg ata tgg gat gaa gat gaa cgt cca cat aga tat gaa      2462
Ser Leu Ser Met Ile Trp Asp Glu Asp Glu Arg Pro His Arg Tyr Glu
    695                 700                 705

tca gaa gat gtt gaa gtg ctt gaa gcc ctc aaa cca cac tcc aat ctg      2510
Ser Glu Asp Val Glu Val Leu Glu Ala Leu Lys Pro His Ser Asn Leu
710                 715                 720                 725

act tgt tta aca att att ggc ttc aga gga atc cgt ctc cca gac tgg      2558
Thr Cys Leu Thr Ile Ile Gly Phe Arg Gly Ile Arg Leu Pro Asp Trp
                730                 735                 740

atg aat cac tca gtt ttg aaa aat gtt gtc tct ctt gaa atc agc gat      2606
Met Asn His Ser Val Leu Lys Asn Val Val Ser Leu Glu Ile Ser Asp
            745                 750                 755

tgc aaa aac tgc tca tgc tta cca ccc ttt ggt gaa ctg cct tgt cta      2654
Cys Lys Asn Cys Ser Cys Leu Pro Pro Phe Gly Glu Leu Pro Cys Leu
        760                 765                 770

aat agt cta cag tta tgg agt ggg tct gca gaa gtg gag tat att gat      2702
Asn Ser Leu Gln Leu Trp Ser Gly Ser Ala Glu Val Glu Tyr Ile Asp
    775                 780                 785

tct gga ttc cct aca aga aga agg ttt cca tct ctg aga aaa ctt att      2750
Ser Gly Phe Pro Thr Arg Arg Arg Phe Pro Ser Leu Arg Lys Leu Ile
790                 795                 800                 805

ata ggc gaa ttt gat aat ctg aaa gga ttg gtg aaa aag gaa gga gaa      2798
Ile Gly Glu Phe Asp Asn Leu Lys Gly Leu Val Lys Lys Glu Gly Glu
                810                 815                 820

gag caa ttc cct gtg ctt gaa gag atg gag att aac tgg tgc cct atg      2846
Glu Gln Phe Pro Val Leu Glu Glu Met Glu Ile Asn Trp Cys Pro Met
            825                 830                 835

ttt gtt att ccg acc ctt tct tct gtc aac aaa ttg gta gtt agt ggg      2894
Phe Val Ile Pro Thr Leu Ser Ser Val Asn Lys Leu Val Val Ser Gly
        840                 845                 850

gaa gag tca gat gca ata ggc ttc agt tcc ata tct aat ctc agg gct      2942
Glu Glu Ser Asp Ala Ile Gly Phe Ser Ser Ile Ser Asn Leu Arg Ala
    855                 860                 865

ctt act tct ctc aat att agc tat aac tct gaa gct act tca ctc cca      2990
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Leu Thr Ser Leu Asn Ile Ser Tyr Asn Ser Glu Ala Thr Ser Leu Pro
870                 875                 880                 885

gaa gag atg ttc aaa agc ctt gca aat cta aaa tac ttg aat atc tat     3038
Glu Glu Met Phe Lys Ser Leu Ala Asn Leu Lys Tyr Leu Asn Ile Tyr
                890                 895                 900

tac ttc aag aat ctc aaa gag ctg cct acc aac ctg gct agt ctt aat     3086
Tyr Phe Lys Asn Leu Lys Glu Leu Pro Thr Asn Leu Ala Ser Leu Asn
            905                 910                 915

gct ttg aag aat ctg gaa att gaa agt tgt tat gca cta gag agt ctc     3134
Ala Leu Lys Asn Leu Glu Ile Glu Ser Cys Tyr Ala Leu Glu Ser Leu
        920                 925                 930

ccc gag gaa ggt gtg aaa ggt tta act tca ctt aca caa tta tcc ata     3182
Pro Glu Glu Gly Val Lys Gly Leu Thr Ser Leu Thr Gln Leu Ser Ile
    935                 940                 945

aca tac tgc acg atg cta caa tgt tta tcg gag gga ttg cag cac cta     3230
Thr Tyr Cys Thr Met Leu Gln Cys Leu Ser Glu Gly Leu Gln His Leu
950                 955                 960                 965

aca gcc ctc aca aat tta tca gtt agg gat tgt cca aca ctg gcc aag     3278
Thr Ala Leu Thr Asn Leu Ser Val Arg Asp Cys Pro Thr Leu Ala Lys
                970                 975                 980

cga tgt gag aag gga ata gga gaa gac tgg tac aaa att gct cac att     3326
Arg Cys Glu Lys Gly Ile Gly Glu Asp Trp Tyr Lys Ile Ala His Ile
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cct gat gtg  ttt atc cgt taa                                       3347
Pro Asp Val  Phe Ile Arg
        1000
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Ile Gln Gly Glu Val Gly Leu Ile Leu Gly Phe Lys Asp Glu Phe Glu
            20                  25                  30

Lys Leu Gln Ser Thr Phe Thr Thr Ile Gln Ala Val Leu Glu Asp Ala
        35                  40                  45

Gln Lys Lys Gln Leu Lys Asp Lys Ala Ile Glu Asn Trp Leu Gln Lys
    50                  55                  60

Leu Asn Ala Ala Val Tyr Glu Ala Asp Asp Ile Leu Asp Glu Cys Lys
65                  70                  75                  80
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Thr Glu Ala Pro Ile Arg Gln Lys Lys Asn Lys Tyr Gly Cys Tyr His
85 90 95

Pro Asn Val Ile Ala Phe Arg His Lys Ile Gly Lys Arg Met Lys Lys
100 105 110

Ile Met Glu Lys Leu Asp Val Ile Ala Ala Glu Arg Ile Lys Phe His
115 120 125

Leu Ala Glu Arg Thr Thr Glu Arg Gln Val Ala Thr Arg Gln Thr Gly
130 135 140

Ala His Leu Arg Tyr Phe Ser Leu Thr Pro Thr Glu Leu Gly Pro Gly
145 150 155 160

Phe Val Leu Asn Glu Pro Gln Val Tyr Gly Arg Asp Lys Glu Lys Asp
165 170 175

Glu Ile Val Lys Ile Leu Ile Asn Ile Val Ser Asp Ala Gln Thr Leu
180 185 190

Ser Val Leu Pro Ile Leu Gly Met Gly Gly Leu Gly Lys Thr Thr Leu
195 200 205

Ala Gln Met Val Phe Asn Asp Gln Arg Val Ile Glu His Phe Leu Pro
210 215 220

Lys Ile Trp Ile Cys Val Ser Glu Asp Phe Asn Glu Lys Arg Leu Ile
225 230 235 240

Lys Glu Ile Val Glu Ser Ile Glu Glu Lys Ser Leu Gly Asp Met Asp
245 250 255

Leu Ala Pro Leu Gln Lys Lys Leu Gln Asp Leu Leu Asn Gly Lys Lys
260 265 270

Tyr Leu Leu Val Leu Asp Asp Ile Trp Asn Glu Asp Gln Asp Lys Trp
275 280 285

Ala Lys Leu Arg Glu Val Leu Lys Val Gly Ala Ser Gly Ala Ser Ile
290 295 300

Leu Thr Thr Thr Arg Leu Glu Lys Val Gly Ser Ile Met Gln Thr Leu
305 310 315 320

Gln Pro Tyr Glu Leu Ser Asn Leu Cys Gln Glu Asp Cys Trp Leu Leu
325 330 335

Phe Met Gln Arg Ala Phe Gly His Gln Glu Glu Ile Asn His Asn Leu
340 345 350

Val Ala Ile Gly Lys Glu Ile Val Lys Lys Cys Gly Gly Val Pro Leu
355 360 365

Ala Ala Lys Thr Leu Gly Gly Ile Leu Arg Phe Lys Arg Gln Glu Arg
370 375 380

Gln Trp Glu His Val Arg Asp Ser Glu Ile Trp Lys Leu Pro Gln Glu
385 390 395 400

Glu Ser Ser Ile Leu Pro Ala Leu Lys Leu Ser Tyr His His Leu Pro
405 410 415

Leu Asp Leu Arg Gln Cys Phe Ser Tyr Cys Ala Val Phe Pro Lys Asp
420 425 430

Thr Lys Met Glu Lys Glu Asn Leu Ile Ser Leu Trp Met Ala His Gly
435 440 445

Phe Leu Leu Ser Lys Gly Asn Leu Glu Leu Glu Asp Val Gly Asn Glu
450 455 460

Val Trp Asn Glu Leu Tyr Leu Arg Ser Phe Phe Gln Glu Ile Glu Val
465 470 475 480

Thr Tyr Gly Lys Thr Tyr Phe Lys Met His Asp Leu Ile His Asp Leu
485 490 495

Ala Thr Ser Leu Phe Ser Ala Ser Ala Ser Ser Asn Asn Ile Arg Glu
500 505 510

Ile Asn Val Lys Gly Tyr Pro His Met Met Ser Ile Gly Phe Ala Lys
515 520 525

Val Val Ser Phe Tyr Ser Arg Ser His Phe Gln Lys Phe Val Ser Leu
530 535 540

Arg Val Leu Asn Leu Ser Asn Leu Glu Leu Lys Gln Leu Pro Ser Ser
545 550 555 560

Ile Gly Asp Leu Val His Leu Arg Tyr Leu Asn Leu Ser Asp Asn Asn
565 570 575

Arg Ile Arg Ser Leu Pro Lys Gln Leu Cys Lys Leu Gln Asn Leu Gln
580 585 590

Thr Leu Asp Leu Arg Cys Cys Tyr Arg Leu Ser Cys Leu Pro Lys Glu
595 600 605

Thr Ser Lys Leu Gly Ser Leu Arg Asn Leu Leu Leu Asp Arg Cys His
610 615 620

Gly Leu Thr Cys Met Pro Pro Arg Ile Gly Ser Leu Thr Cys Leu Lys
625 630 635 640

Thr Leu Asp Arg Phe Ala Met Gly Arg Glu Lys Ser Pro Gln Ile Gly
645 650 655

Glu Leu Arg Asn Leu Asn Leu Tyr Gly Ser Ile Ser Ile Thr His Leu
660 665 670

Glu Arg Val Lys Asn Asp Met Asp Ala Lys Glu Ala Asn Leu Ser Ser
675 680 685

Lys Glu Asn Leu His Ser Leu Ser Met Ile Trp Asp Glu Asp Glu Arg
690 695 700

Pro His Arg Tyr Glu Ser Glu Asp Val Glu Val Leu Glu Ala Leu Lys
705 710 715 720

Pro His Ser Asn Leu Thr Cys Leu Thr Ile Ile Gly Phe Arg Gly Ile
725 730 735

Arg Leu Pro Asp Trp Met Asn His Ser Val Leu Lys Asn Val Val Ser
740 745 750

Leu Glu Ile Ser Asp Cys Lys Asn Cys Ser Cys Leu Pro Pro Phe Gly
755 760 765

Glu Leu Pro Cys Leu Asn Ser Leu Gln Leu Trp Ser Gly Ser Ala Glu
770 775 780

Val Glu Tyr Ile Asp Ser Gly Phe Pro Thr Arg Arg Arg Phe Pro Ser
785 790 795 800

Leu Arg Lys Leu Ile Ile Gly Glu Phe Asp Asn Leu Lys Gly Leu Val

805 810 815

Lys Lys Glu Gly Glu Glu Gln Phe Pro Val Leu Glu Glu Met Glu Ile
820 825 830

Asn Trp Cys Pro Met Phe Val Ile Pro Thr Leu Ser Ser Val Asn Lys
835 840 845

Leu Val Val Ser Gly Glu Glu Ser Asp Ala Ile Gly Phe Ser Ser Ile
850 855 860

Ser Asn Leu Arg Ala Leu Thr Ser Leu Asn Ile Ser Tyr Asn Ser Glu
865 870 875 880

Ala Thr Ser Leu Pro Glu Glu Met Phe Lys Ser Leu Ala Asn Leu Lys
885 890 895

Tyr Leu Asn Ile Tyr Tyr Phe Lys Asn Leu Lys Glu Leu Pro Thr Asn
900 905 910

Leu Ala Ser Leu Asn Ala Leu Lys Asn Leu Glu Ile Glu Ser Cys Tyr
915 920 925

Ala Leu Glu Ser Leu Pro Glu Glu Gly Val Lys Gly Leu Thr Ser Leu
930 935 940

Thr Gln Leu Ser Ile Thr Tyr Cys Thr Met Leu Gln Cys Leu Ser Glu
945 950 955 960

Gly Leu Gln His Leu Thr Ala Leu Thr Asn Leu Ser Val Arg Asp Cys
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Ile Gln Gly Glu Leu Val Leu Leu Phe Gly Phe Glu Asn Asp Phe Arg
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Lys Leu Ser Ser Thr Phe Ser Thr Ile Gln Leu Val Leu Glu Asp Ala
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Ser Glu Lys Gln Leu Lys Asp Lys Ala Ile Glu Asn Trp Leu Gln Lys
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Leu Asn Phe Ala Ala Tyr Glu Val Asp Asp Ile Leu Asp Glu Cys Lys
65 70 75 80

aat gag gca gca aga ttc aat cag tcc tta tta ggg tat att cat cca 345
Asn Glu Ala Ala Arg Phe Asn Gln Ser Leu Leu Gly Tyr Ile His Pro
85 90 95

aag atc atc att ttt cgt tac aag ctc gga aaa aga atg aaa aga atg 393
Lys Ile Ile Ile Phe Arg Tyr Lys Leu Gly Lys Arg Met Lys Arg Met
100 105 110

atg gag aaa cta gat gca att gct gac gaa aga agg aag ttt cat ttg 441
Met Glu Lys Leu Asp Ala Ile Ala Asp Glu Arg Arg Lys Phe His Leu
115 120 125

cgt gca aag att gtc gag aaa caa gct tct aaa cgt gaa aca ggt gct 489
Arg Ala Lys Ile Val Glu Lys Gln Ala Ser Lys Arg Glu Thr Gly Ala
130 135 140

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His Leu Lys Leu Cys Leu Ala Lys Tyr Leu Leu Ile Ala
145 150 155

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Thr Gly Phe Val Leu Ala Glu
160

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Pro Lys Val Tyr Gly Arg Asp Lys Glu Lys Asp Glu Met Val Lys Ile

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165                 170                 175                 180

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Leu Ile Asn Ser Val Ser Asn Ala Gln Glu Leu Leu Val Leu Pro Ile
                185                 190                 195

ctt ggt atg ggg gga cta gga aag aca aca ctt gcc caa atg att ttt      855
Leu Gly Met Gly Gly Leu Gly Lys Thr Thr Leu Ala Gln Met Ile Phe
            200                 205                 210

aat gat cag agc gtg act gca cat ttc aat cta aag ata tgg gtt tgt      903
Asn Asp Gln Ser Val Thr Ala His Phe Asn Leu Lys Ile Trp Val Cys
        215                 220                 225

gtc tca gat gat ttt gat gag aag agg ttg ata aag gca att gta gaa      951
Val Ser Asp Asp Phe Asp Glu Lys Arg Leu Ile Lys Ala Ile Val Glu
    230                 235                 240

tct att gaa aga agg cca ctt ggt gac ata gac ttg gct ccc ctc cag      999
Ser Ile Glu Arg Arg Pro Leu Gly Asp Ile Asp Leu Ala Pro Leu Gln
245                 250                 255                 260

aag aag ctt cag gag ttg ttg aat gga aaa aga tac ttt ctt gtt tta     1047
Lys Lys Leu Gln Glu Leu Leu Asn Gly Lys Arg Tyr Phe Leu Val Leu
                265                 270                 275

gat gat gtt tgg aat gaa gat caa gaa aag tgg gct aag ata aaa gca     1095
Asp Asp Val Trp Asn Glu Asp Gln Glu Lys Trp Ala Lys Ile Lys Ala
            280                 285                 290

gtc tta aag gtt gga gca caa ggt tct tct att cta gcc act act cgt     1143
Val Leu Lys Val Gly Ala Gln Gly Ser Ser Ile Leu Ala Thr Thr Arg
        295                 300                 305

ctt gaa agg gtc gga tca att atg gga act tgg caa cca tat cag tta     1191
Leu Glu Arg Val Gly Ser Ile Met Gly Thr Trp Gln Pro Tyr Gln Leu
    310                 315                 320

tca att ttg tct cca gaa tat tgt tgg ttg ttg ttc aag caa cgt gca     1239
Ser Ile Leu Ser Pro Glu Tyr Cys Trp Leu Leu Phe Lys Gln Arg Ala
325                 330                 335                 340

ttt ggc cac caa acg gaa aca aat cct gcc ctt gtg ggg att gga aaa     1287
Phe Gly His Gln Thr Glu Thr Asn Pro Ala Leu Val Gly Ile Gly Lys
                345                 350                 355

gag att gtg aag aaa tgt ggg ggt gtg cct cta gca gcc aag act ctt     1335
Glu Ile Val Lys Lys Cys Gly Gly Val Pro Leu Ala Ala Lys Thr Leu
            360                 365                 370

gga ggt ctt tta cgc ttc aag aga gaa gaa agt gaa tgg gaa cat gtg     1383
Gly Gly Leu Leu Arg Phe Lys Arg Glu Glu Ser Glu Trp Glu His Val
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aaa gat agt gag att tgg aat tta cct caa gat gaa aat tct gtt ttg     1431
Lys Asp Ser Glu Ile Trp Asn Leu Pro Gln Asp Glu Asn Ser Val Leu
    390                 395                 400

cct tcc ctg agg ctg agt tat cat cac ctt cca ctt aat ttg aga caa     1479
Pro Ser Leu Arg Leu Ser Tyr His His Leu Pro Leu Asn Leu Arg Gln
405                 410                 415                 420
```

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tgt ttt gca tat tgt gcg gta ttc cca aag gac acc aaa ata gaa aag     1527
Cys Phe Ala Tyr Cys Ala Val Phe Pro Lys Asp Thr Lys Ile Glu Lys
                425                 430                 435

gaa tat ctc atc act ctc tgg atg gca cat ggt ttt ctt tta tca aaa     1575
Glu Tyr Leu Ile Thr Leu Trp Met Ala His Gly Phe Leu Leu Ser Lys
            440                 445                 450

gaa aat tca gag cta gag gat gtg ggt aat gaa gta tgg aaa gaa tta     1623
Glu Asn Ser Glu Leu Glu Asp Val Gly Asn Glu Val Trp Lys Glu Leu
        455                 460                 465

tac ttg agg tct ttc ttc caa gag gtc gaa gaa tat aaa ttt ggt aat     1671
Tyr Leu Arg Ser Phe Phe Gln Glu Val Glu Glu Tyr Lys Phe Gly Asn
    470                 475                 480

act tat ttc aag atg cat gat ctc atc cac gat ttg gct aca tct ctg     1719
Thr Tyr Phe Lys Met His Asp Leu Ile His Asp Leu Ala Thr Ser Leu
485                 490                 495                 500

ttc tca aca aac aca agg agc agc aaa att cgt caa ata aga gta gca     1767
Phe Ser Thr Asn Thr Arg Ser Ser Lys Ile Arg Gln Ile Arg Val Ala
                505                 510                 515

cag aaa aat aca att cct att ggt ttt gct gaa gtg gtg cct tct tat     1815
Gln Lys Asn Thr Ile Pro Ile Gly Phe Ala Glu Val Val Pro Ser Tyr
            520                 525                 530

tct cct tta atc ttt aaa agg ttt gtc tcg cta agg gtt ctt gat atg     1863
Ser Pro Leu Ile Phe Lys Arg Phe Val Ser Leu Arg Val Leu Asp Met
        535                 540                 545

aaa ttt tca aag ttt gat cag tta tca tct tcc atc gga gat cta ata     1911
Lys Phe Ser Lys Phe Asp Gln Leu Ser Ser Ser Ile Gly Asp Leu Ile
    550                 555                 560

cat tta agg ttg ttg aac ttg cgt ggc agt agc att cgt agc ctt cca     1959
His Leu Arg Leu Leu Asn Leu Arg Gly Ser Ser Ile Arg Ser Leu Pro
565                 570                 575                 580

aag agg tta tgc aag ctt caa aat ctg cag aca ctt gat ata tca tgt     2007
Lys Arg Leu Cys Lys Leu Gln Asn Leu Gln Thr Leu Asp Ile Ser Cys
                585                 590                 595

tgt ttc tca ctt tct tat att cca aaa caa ata agt aaa tta agt agt     2055
Cys Phe Ser Leu Ser Tyr Ile Pro Lys Gln Ile Ser Lys Leu Ser Ser
            600                 605                 610

ctt aga aat ctt gtg ttc agt ggt tgt caa ata act tct atg cca cca     2103
Leu Arg Asn Leu Val Phe Ser Gly Cys Gln Ile Thr Ser Met Pro Pro
        615                 620                 625

aga ata gga tca ttg aca tgc ctt aag act cta gat tac ttt att gtc     2151
Arg Ile Gly Ser Leu Thr Cys Leu Lys Thr Leu Asp Tyr Phe Ile Val
    630                 635                 640

ggc gag agg aaa ggt tat caa ctt ggt gaa cta cgg aat cta agc cta     2199
Gly Glu Arg Lys Gly Tyr Gln Leu Gly Glu Leu Arg Asn Leu Ser Leu
645                 650                 655                 660
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cat ggt tca ctt tca atc tca cat ctt gag aga gtg aag agt gaa acg     2247
His Gly Ser Leu Ser Ile Ser His Leu Glu Arg Val Lys Ser Glu Thr
                665                 670                 675

gat gca aaa gaa gct aat tta tct acc aaa caa aaa ttg tac aat tta     2295
Asp Ala Lys Glu Ala Asn Leu Ser Thr Lys Gln Lys Leu Tyr Asn Leu
            680                 685                 690

tgc atg agt tgg gat att agg cca tat gga tat gaa tca gaa aac aat     2343
Cys Met Ser Trp Asp Ile Arg Pro Tyr Gly Tyr Glu Ser Glu Asn Asn
        695                 700                 705

ttg gat gaa aaa gtg ctt gaa gcc ctc aga cca cac tcc aac ctg aaa     2391
Leu Asp Glu Lys Val Leu Glu Ala Leu Arg Pro His Ser Asn Leu Lys
    710                 715                 720

tca cta aag ctc att ggc ttc aga ggt ttt cat ttt cca aat tgg atg     2439
Ser Leu Lys Leu Ile Gly Phe Arg Gly Phe His Phe Pro Asn Trp Met
725                 730                 735                 740

aac gct tcg gtt ttg aaa aat gtc gtc tct att gaa att gaa tgt gaa     2487
Asn Ala Ser Val Leu Lys Asn Val Val Ser Ile Glu Ile Glu Cys Glu
                745                 750                 755

aac tgc tgg cgt tta cca cca ttt gga gag ctg cct tgt cta gaa agt     2535
Asn Cys Trp Arg Leu Pro Pro Phe Gly Glu Leu Pro Cys Leu Glu Ser
            760                 765                 770

cta aag tta tac aac gga tct gcg gag gtg gag tat att gaa gag gat     2583
Leu Lys Leu Tyr Asn Gly Ser Ala Glu Val Glu Tyr Ile Glu Glu Asp
        775                 780                 785

gat ggt cat tcc aca tta aag ttc cca tac ttg aaa cga ctt gct att     2631
Asp Gly His Ser Thr Leu Lys Phe Pro Tyr Leu Lys Arg Leu Ala Ile
    790                 795                 800

gaa aga ttt cca aat ctg aaa gga ctg ctg aga agt gaa gga gaa gag     2679
Glu Arg Phe Pro Asn Leu Lys Gly Leu Leu Arg Ser Glu Gly Glu Glu
805                 810                 815                 820

aaa ttc tcc atg ctt gaa gaa atg gaa att tgg cat tgc cct atg ttt     2727
Lys Phe Ser Met Leu Glu Glu Met Glu Ile Trp His Cys Pro Met Phe
                825                 830                 835

gtt ttt cca gca ttc tct tct gtc acg aaa ttg gat gtc tgg ggg gaa     2775
Val Phe Pro Ala Phe Ser Ser Val Thr Lys Leu Asp Val Trp Gly Glu
            840                 845                 850

ata gat gca gca agt ctt agc tcc ata tct aag ctt acc act ctt acg     2823
Ile Asp Ala Ala Ser Leu Ser Ser Ile Ser Lys Leu Thr Thr Leu Thr
        855                 860                 865

tct ctc tct att gat cat aac ttt gaa gca aca act ctc cca gaa gag     2871
Ser Leu Ser Ile Asp His Asn Phe Glu Ala Thr Thr Leu Pro Glu Glu
    870                 875                 880

atg ttc aaa cgc ctt gta aat ctt gag tcc ttg agc att ata tac ttc     2919
Met Phe Lys Arg Leu Val Asn Leu Glu Ser Leu Ser Ile Ile Tyr Phe
885                 890                 895                 900

aaa aaa ctc aga gag ttg cca agc agc ctg gct agc ctc aat gct ttg     2967
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Lys Lys Leu Arg Glu Leu Pro Ser Ser Leu Ala Ser Leu Asn Ala Leu
                905                 910                 915

aag tgt cta aaa att cat tat tgt tac gca cta gag agt ctc ccc gaa     3015
Lys Cys Leu Lys Ile His Tyr Cys Tyr Ala Leu Glu Ser Leu Pro Glu
            920                 925                 930

caa ggg atg gaa ggg tta act tca ctc acc gac tta tat gtt caa aac     3063
Gln Gly Met Glu Gly Leu Thr Ser Leu Thr Asp Leu Tyr Val Gln Asn
        935                 940                 945

tgt gag atg cta aaa tgt tta cct gag gga ttg cag cac cta aga gcc     3111
Cys Glu Met Leu Lys Cys Leu Pro Glu Gly Leu Gln His Leu Arg Ala
    950                 955                 960

ctc act agt tta caa att tat ggc tgt cca gca ttg aaa aag cgg tgt     3159
Leu Thr Ser Leu Gln Ile Tyr Gly Cys Pro Ala Leu Lys Lys Arg Cys
965                 970                 975                 980

gcg aag ggg ata gga gag gac tgg cac aaa att gct cac att cct aat     3207
Ala Lys Gly Ile Gly Glu Asp Trp His Lys Ile Ala His Ile Pro Asn
                985                 990                 995

gta gat att tgt  tag                                               3222
Val Asp Ile Cys
            1000
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<213> Solanum Bulbocastanum

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Met Ala Glu Ala Phe Leu Gln Val Leu Leu Gly Asn Ile Thr Ser Phe
1               5                   10                  15

Ile Gln Gly Glu Leu Val Leu Leu Phe Gly Phe Glu Asn Asp Phe Arg
            20                  25                  30

Lys Leu Ser Ser Thr Phe Ser Thr Ile Gln Leu Val Leu Glu Asp Ala
        35                  40                  45

Ser Glu Lys Gln Leu Lys Asp Lys Ala Ile Glu Asn Trp Leu Gln Lys
    50                  55                  60

Leu Asn Phe Ala Ala Tyr Glu Val Asp Asp Ile Leu Asp Glu Cys Lys
65                  70                  75                  80

Asn Glu Ala Ala Arg Phe Asn Gln Ser Leu Leu Gly Tyr Ile His Pro
                85                  90                  95

Lys Ile Ile Ile Phe Arg Tyr Lys Leu Gly Lys Arg Met Lys Arg Met
            100                 105                 110
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Met Glu Lys Leu Asp Ala Ile Ala Asp Glu Arg Arg Lys Phe His Leu
        115                 120                 125

Arg Ala Lys Ile Val Glu Lys Gln Ala Ser Lys Arg Glu Thr Gly Ala
    130                 135                 140

His Leu Lys Leu Cys Leu Ala Lys Tyr Leu Leu Ile Ala Thr Gly Phe
145                 150                 155                 160

Val Leu Ala Glu Pro Lys Val Tyr Gly Arg Asp Lys Glu Lys Asp Glu
                165                 170                 175

Met Val Lys Ile Leu Ile Asn Ser Val Ser Asn Ala Gln Glu Leu Leu
            180                 185                 190

Val Leu Pro Ile Leu Gly Met Gly Gly Leu Gly Lys Thr Thr Leu Ala
        195                 200                 205

Gln Met Ile Phe Asn Asp Gln Ser Val Thr Ala His Phe Asn Leu Lys
    210                 215                 220

Ile Trp Val Cys Val Ser Asp Asp Phe Asp Glu Lys Arg Leu Ile Lys
225                 230                 235                 240

Ala Ile Val Glu Ser Ile Glu Arg Arg Pro Leu Gly Asp Ile Asp Leu
                245                 250                 255

Ala Pro Leu Gln Lys Lys Leu Gln Glu Leu Leu Asn Gly Lys Arg Tyr
            260                 265                 270

Phe Leu Val Leu Asp Asp Val Trp Asn Glu Asp Gln Glu Lys Trp Ala
        275                 280                 285

Lys Ile Lys Ala Val Leu Lys Val Gly Ala Gln Gly Ser Ser Ile Leu
    290                 295                 300

Ala Thr Thr Arg Leu Glu Arg Val Gly Ser Ile Met Gly Thr Trp Gln
305                 310                 315                 320

Pro Tyr Gln Leu Ser Ile Leu Ser Pro Glu Tyr Cys Trp Leu Leu Phe
                325                 330                 335

Lys Gln Arg Ala Phe Gly His Gln Thr Glu Thr Asn Pro Ala Leu Val
            340                 345                 350
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Gly Ile Gly Lys Glu Ile Val Lys Lys Cys Gly Gly Val Pro Leu Ala
        355                 360                 365

Ala Lys Thr Leu Gly Gly Leu Leu Arg Phe Lys Arg Glu Glu Ser Glu
    370                 375                 380

Trp Glu His Val Lys Asp Ser Glu Ile Trp Asn Leu Pro Gln Asp Glu
385                 390                 395                 400

Asn Ser Val Leu Pro Ser Leu Arg Leu Ser Tyr His His Leu Pro Leu
                405                 410                 415

Asn Leu Arg Gln Cys Phe Ala Tyr Cys Ala Val Phe Pro Lys Asp Thr
            420                 425                 430

Lys Ile Glu Lys Glu Tyr Leu Ile Thr Leu Trp Met Ala His Gly Phe
        435                 440                 445

Leu Leu Ser Lys Glu Asn Ser Glu Leu Glu Asp Val Gly Asn Glu Val
    450                 455                 460

Trp Lys Glu Leu Tyr Leu Arg Ser Phe Phe Gln Glu Val Glu Glu Tyr
465                 470                 475                 480

Lys Phe Gly Asn Thr Tyr Phe Lys Met His Asp Leu Ile His Asp Leu
                485                 490                 495

Ala Thr Ser Leu Phe Ser Thr Asn Thr Arg Ser Ser Lys Ile Arg Gln
            500                 505                 510

Ile Arg Val Ala Gln Lys Asn Thr Ile Pro Ile Gly Phe Ala Glu Val
        515                 520                 525

Val Pro Ser Tyr Ser Pro Leu Ile Phe Lys Arg Phe Val Ser Leu Arg
    530                 535                 540

Val Leu Asp Met Lys Phe Ser Lys Phe Asp Gln Leu Ser Ser Ser Ile
545                 550                 555                 560

Gly Asp Leu Ile His Leu Arg Leu Leu Asn Leu Arg Gly Ser Ser Ile
                565                 570                 575

Arg Ser Leu Pro Lys Arg Leu Cys Lys Leu Gln Asn Leu Gln Thr Leu
            580                 585                 590
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Asp Ile Ser Cys Cys Phe Ser Leu Ser Tyr Ile Pro Lys Gln Ile Ser
        595                 600                 605

Lys Leu Ser Ser Leu Arg Asn Leu Val Phe Ser Gly Cys Gln Ile Thr
    610                 615                 620

Ser Met Pro Pro Arg Ile Gly Ser Leu Thr Cys Leu Lys Thr Leu Asp
625                 630                 635                 640

Tyr Phe Ile Val Gly Glu Arg Lys Gly Tyr Gln Leu Gly Glu Leu Arg
                645                 650                 655

Asn Leu Ser Leu His Gly Ser Leu Ser Ile Ser His Leu Glu Arg Val
            660                 665                 670

Lys Ser Glu Thr Asp Ala Lys Glu Ala Asn Leu Ser Thr Lys Gln Lys
        675                 680                 685

Leu Tyr Asn Leu Cys Met Ser Trp Asp Ile Arg Pro Tyr Gly Tyr Glu
    690                 695                 700

Ser Glu Asn Asn Leu Asp Glu Lys Val Leu Glu Ala Leu Arg Pro His
705                 710                 715                 720

Ser Asn Leu Lys Ser Leu Lys Leu Ile Gly Phe Arg Gly Phe His Phe
                725                 730                 735

Pro Asn Trp Met Asn Ala Ser Val Leu Lys Asn Val Val Ser Ile Glu
            740                 745                 750

Ile Glu Cys Glu Asn Cys Trp Arg Leu Pro Pro Phe Gly Glu Leu Pro
        755                 760                 765

Cys Leu Glu Ser Leu Lys Leu Tyr Asn Gly Ser Ala Glu Val Glu Tyr
    770                 775                 780

Ile Glu Glu Asp Asp Gly His Ser Thr Leu Lys Phe Pro Tyr Leu Lys
785                 790                 795                 800

Arg Leu Ala Ile Glu Arg Phe Pro Asn Leu Lys Gly Leu Leu Arg Ser
                805                 810                 815

Glu Gly Glu Glu Lys Phe Ser Met Leu Glu Glu Met Glu Ile Trp His
            820                 825                 830

Cys Pro Met Phe Val Phe Pro Ala Phe Ser Ser Val Thr Lys Leu Asp
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        835                 840                 845

Val Trp Gly Glu Ile Asp Ala Ala Ser Leu Ser Ser Ile Ser Lys Leu
    850                 855                 860

Thr Thr Leu Thr Ser Leu Ser Ile Asp His Asn Phe Glu Ala Thr Thr
865                 870                 875                 880

Leu Pro Glu Glu Met Phe Lys Arg Leu Val Asn Leu Glu Ser Leu Ser
                885                 890                 895

Ile Ile Tyr Phe Lys Lys Leu Arg Glu Leu Pro Ser Ser Leu Ala Ser
            900                 905                 910

Leu Asn Ala Leu Lys Cys Leu Lys Ile His Tyr Cys Tyr Ala Leu Glu
        915                 920                 925

Ser Leu Pro Glu Gln Gly Met Glu Gly Leu Thr Ser Leu Thr Asp Leu
    930                 935                 940

Tyr Val Gln Asn Cys Glu Met Leu Lys Cys Leu Pro Glu Gly Leu Gln
945                 950                 955                 960

His Leu Arg Ala Leu Thr Ser Leu Gln Ile Tyr Gly Cys Pro Ala Leu
                965                 970                 975

Lys Lys Arg Cys Ala Lys Gly Ile Gly Glu Asp Trp His Lys Ile Ala
            980                 985                 990

His Ile Pro Asn Val Asp Ile Cys
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<222> (1029)..(1459)

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taaatacata tatctggtat ataattaatt ttttaaagtc atgaagtatg tatcaaatac 180

acatatggaa aaaattaact attcataatt taaaaaatag aaaagataca tctagtgaaa 240

ttaggtgcat gtatcaaata cattaggaaa agggcatata tcttgatcta gataattaac 300

gattttgatt tatgtataat ttccaaatga aggtttatat ctacttcaga aataacaata 360

tacttttatc agaacattca acaaagcaac aaccaactag agtgaaaaat acacattgtt 420

ctctagacat acaaaattga gaaaagaatc tcaaaattta gagaaacaaa tctgaatttc 480

tagaagaaaa aaataattat gcactttgct attgctcgaa aaataaatga aagaaattag 540

actttttaa aagatgttag actagatata ctcaaaagct attaaaggag taatattctt 600

cttacattaa gtattttagt tacagtcctg taattaaaga cacattttag attgtatcta 660

aacttaaatg tatctagaat acatatattt gaatgcatca tatacatgta tccgacacac 720

caattctcat aaaaaacgta atatcctaaa ctaatttatc cttcaagtca acttaagccc 780

aatatacatt ttcatctcta aaggcccaag tggcacaaaa tgtcaggccc aattacgaag 840

aaaagggctt gtaaaaccct aataaagtgg cactggcaga gcttacactc tcattccatc 900

aacaaagaaa ccctaaaagc cgcagcgcca ctgatttctc tcctccaggc gaaggatccc 960

cgggggatcc ccccaacatc ttacttcatt tcaaaaaata tagattcatt gcgtactcac 1020

aatactct atg gct gaa gct ttc ctt caa gtt ctg tta gac aat ctg act 1070
Met Ala Glu Ala Phe Leu Gln Val Leu Leu Asp Asn Leu Thr
1 5 10

tgt ttc atc caa ggg gaa ctt gga ttg att ctt ggt ttt aag gat gag 1118
Cys Phe Ile Gln Gly Glu Leu Gly Leu Ile Leu Gly Phe Lys Asp Glu
15 20 25 30

ttc gaa aag ctt caa agc acg ttt act aca atc caa gct gtg cta gaa 1166
Phe Glu Lys Leu Gln Ser Thr Phe Thr Thr Ile Gln Ala Val Leu Glu
35 40 45

gat gct cag aag aag caa ttg aag gac aag gca ata gaa aat tgg ttg 1214
Asp Ala Gln Lys Lys Gln Leu Lys Asp Lys Ala Ile Glu Asn Trp Leu
50 55 60

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cag aaa ctc aat gct gct gca tat gag gct gat gac atc ttg gac gaa      1262
Gln Lys Leu Asn Ala Ala Ala Tyr Glu Ala Asp Asp Ile Leu Asp Glu
        65                  70                  75

tgt aaa act gag gca cca att aga cag aag aag aac aaa tat ggg tgt      1310
Cys Lys Thr Glu Ala Pro Ile Arg Gln Lys Lys Asn Lys Tyr Gly Cys
    80                  85                  90

tat cat cca aac gtt atc act ttt cgt cac aag att ggg aaa agg atg      1358
Tyr His Pro Asn Val Ile Thr Phe Arg His Lys Ile Gly Lys Arg Met
95                  100                 105                 110

aaa aag att atg gag aaa cta gat gta att gca gcg gaa cga att aag      1406
Lys Lys Ile Met Glu Lys Leu Asp Val Ile Ala Ala Glu Arg Ile Lys
                115                 120                 125

ttt cat ttg gat gaa agg act ata gag aga caa gtt gct aca cgc caa      1454
Phe His Leu Asp Glu Arg Thr Ile Glu Arg Gln Val Ala Thr Arg Gln
            130                 135                 140

aca gg  tgctcatctt agatattttt ctgaaaaaac agctttatat catcaaattc      1509
Thr Gly


atgtgtgttt tgggaattcg tctaatctaa atgttcgtct caagtctaag tagataagtg   1569

gatccagctt tggatttatt aatctattag ctaaatctgt ttagtgaagt ttttaacata   1629

tataacctca gataaatcca tagcttactc ataggattag gataggcccc caagtctaaa   1689

tgacaggata aagccagagt tgttttagct cttataaatt aacaatgata ataatgtgaa   1749

ttcaaaaaag tgcatttttt taatttgaaa tatttctgct gcttctcaag cttatcattg   1809

tctttttact gtgcaaaatt ctactttgta tttttgctga ctcctaccga gcttgggcca   1869

gg t ttt gtt ttg aat gaa cca caa gtt tat gga aga gac aaa gaa aag      1917
     Phe Val Leu Asn Glu Pro Gln Val Tyr Gly Arg Asp Lys Glu Lys
     145                 150                 155

gac gag ata gtg aaa atc ctg ata aac aat gtt agc aat gcc caa aca      1965
Asp Glu Ile Val Lys Ile Leu Ile Asn Asn Val Ser Asn Ala Gln Thr
160                 165                 170                 175

ctt cca gtc ctc cca ata ctt ggt atg ggg gga cta gga aag acg act      2013
Leu Pro Val Leu Pro Ile Leu Gly Met Gly Gly Leu Gly Lys Thr Thr
                180                 185                 190

ctt gcc caa atg gtc ttc aat gat cag aga gta att gag cat ttc cat      2061
Leu Ala Gln Met Val Phe Asn Asp Gln Arg Val Ile Glu His Phe His
            195                 200                 205

ccc aaa ata tgg att tgt gtc tcg gaa gat ttt aat gag aag agg ttg      2109
Pro Lys Ile Trp Ile Cys Val Ser Glu Asp Phe Asn Glu Lys Arg Leu
        210                 215                 220

ata aag gaa att gta gaa tct att gaa gaa aag tca ctt ggt ggc atg      2157
Ile Lys Glu Ile Val Glu Ser Ile Glu Glu Lys Ser Leu Gly Gly Met
    225                 230                 235

gac ttg gct cca ctt caa aag aag ctt cgg gac ttg ctg aat gga aaa      2205
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Asp Leu Ala Pro Leu Gln Lys Lys Leu Arg Asp Leu Leu Asn Gly Lys
240                 245                 250                 255

aaa tat ttg ctc gtc tta gat gat gtt tgg aat gaa gat caa gat aag     2253
Lys Tyr Leu Leu Val Leu Asp Asp Val Trp Asn Glu Asp Gln Asp Lys
                260                 265                 270

tgg gct aag tta aga caa gtc ttg aag gtt gga gca agt ggc gct tct     2301
Trp Ala Lys Leu Arg Gln Val Leu Lys Val Gly Ala Ser Gly Ala Ser
            275                 280                 285

gtt cta acc act act cgt ctt gaa aag gtt gga tca att atg gga aca     2349
Val Leu Thr Thr Thr Arg Leu Glu Lys Val Gly Ser Ile Met Gly Thr
        290                 295                 300

ttg caa cca tat gaa ttg tca aat ttg tct caa gaa gat tgt tgg ttg     2397
Leu Gln Pro Tyr Glu Leu Ser Asn Leu Ser Gln Glu Asp Cys Trp Leu
    305                 310                 315

ttg ttc atg caa cgt gca ttt ggg cac caa gaa gaa ata aat ctt aat     2445
Leu Phe Met Gln Arg Ala Phe Gly His Gln Glu Glu Ile Asn Leu Asn
320                 325                 330                 335

ctt gtg gct atc gga aag gag att gtg aaa aaa tgt ggt ggt gtg cct     2493
Leu Val Ala Ile Gly Lys Glu Ile Val Lys Lys Cys Gly Gly Val Pro
                340                 345                 350

cta gca gct aaa act ctt gga ggt att ttg cgc ttt aag aga gaa gaa     2541
Leu Ala Ala Lys Thr Leu Gly Gly Ile Leu Arg Phe Lys Arg Glu Glu
            355                 360                 365

aga cag tgg gaa cat gtg aga gat agt gag att tgg aaa ttg cct caa     2589
Arg Gln Trp Glu His Val Arg Asp Ser Glu Ile Trp Lys Leu Pro Gln
        370                 375                 380

gaa gaa agt tct att ctg cct gcc ctg aga ctt agt tac cat cac ctt     2637
Glu Glu Ser Ser Ile Leu Pro Ala Leu Arg Leu Ser Tyr His His Leu
    385                 390                 395

cca ctt gat ttg aga caa tgc ttt aca tat tgt gca gta ttc cca aag     2685
Pro Leu Asp Leu Arg Gln Cys Phe Thr Tyr Cys Ala Val Phe Pro Lys
400                 405                 410                 415

gat acc gaa atg gaa aag gga aat cta atc tct ctc tgg atg gca cat     2733
Asp Thr Glu Met Glu Lys Gly Asn Leu Ile Ser Leu Trp Met Ala His
                420                 425                 430

ggt ttt att tta tcg aaa gga aac ttg gag cta gag aat gta ggt aat     2781
Gly Phe Ile Leu Ser Lys Gly Asn Leu Glu Leu Glu Asn Val Gly Asn
            435                 440                 445

gaa gta tgg aat gaa tta tac ttg agg tct ttc ttc caa gag att gaa     2829
Glu Val Trp Asn Glu Leu Tyr Leu Arg Ser Phe Phe Gln Glu Ile Glu
        450                 455                 460

gtt aaa tct ggt caa act tat ttc aag atg cat gat ctc att cat gat     2877
Val Lys Ser Gly Gln Thr Tyr Phe Lys Met His Asp Leu Ile His Asp
    465                 470                 475

ctg gca aca tct cta ttt tcg gca agc aca tca agc agc aat atc cga     2925
Leu Ala Thr Ser Leu Phe Ser Ala Ser Thr Ser Ser Ser Asn Ile Arg
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480                 485                 490                 495

gaa ata att gta gaa aat tac ata cat atg atg tcc att ggt ttc act     2973
Glu Ile Ile Val Glu Asn Tyr Ile His Met Met Ser Ile Gly Phe Thr
                500                 505                 510

aaa gtg gta tct tct tac tct ctt tcc cac ttg cag aag ttt gtc tcg     3021
Lys Val Val Ser Ser Tyr Ser Leu Ser His Leu Gln Lys Phe Val Ser
            515                 520                 525

ttg agg gtg ctt aat cta agt gac ata aaa ctt aag cag tta ccg tct     3069
Leu Arg Val Leu Asn Leu Ser Asp Ile Lys Leu Lys Gln Leu Pro Ser
        530                 535                 540

tcc att gga gat cta gta cat tta aga tac cta aac ttg tct ggc aat     3117
Ser Ile Gly Asp Leu Val His Leu Arg Tyr Leu Asn Leu Ser Gly Asn
    545                 550                 555

act agt att cgt agt ctt cca aac cag tta tgc aag ctt caa aat ctg     3165
Thr Ser Ile Arg Ser Leu Pro Asn Gln Leu Cys Lys Leu Gln Asn Leu
560                 565                 570                 575

cag act ctt gat cta cat ggc tgt cat tca ctt tgt tgt ttg cca aaa     3213
Gln Thr Leu Asp Leu His Gly Cys His Ser Leu Cys Cys Leu Pro Lys
                580                 585                 590

gaa aca agc aaa ctt ggt agt ctt cga aat ctt tta ctt gat ggt tgc     3261
Glu Thr Ser Lys Leu Gly Ser Leu Arg Asn Leu Leu Leu Asp Gly Cys
            595                 600                 605

tat gga ttg act tgt atg cca cca agg ata gga tct ttg aca tgc ctt     3309
Tyr Gly Leu Thr Cys Met Pro Pro Arg Ile Gly Ser Leu Thr Cys Leu
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aag act cta agt aga ttt gtg gtg gga att cag aag aaa agt tgt caa     3357
Lys Thr Leu Ser Arg Phe Val Val Gly Ile Gln Lys Lys Ser Cys Gln
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ctt ggt gaa tta cga aac ctg aat ctc tat ggc tca att gaa atc acg     3405
Leu Gly Glu Leu Arg Asn Leu Asn Leu Tyr Gly Ser Ile Glu Ile Thr
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cat ctt gag aga gtg aag aat gat atg gat gca aaa gaa gcc aat tta     3453
His Leu Glu Arg Val Lys Asn Asp Met Asp Ala Lys Glu Ala Asn Leu
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tct gca aaa gaa aat ctg cat tct tta agc atg aaa tgg gat gac gat     3501
Ser Ala Lys Glu Asn Leu His Ser Leu Ser Met Lys Trp Asp Asp Asp
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gaa cgt cca cgt ata tat gaa tca gaa aaa gtt gaa gtg ctt gaa gct     3549
Glu Arg Pro Arg Ile Tyr Glu Ser Glu Lys Val Glu Val Leu Glu Ala
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ctc aaa cca cac tcc aat ctg act tgt tta aca atc agg ggc ttc aga     3597
Leu Lys Pro His Ser Asn Leu Thr Cys Leu Thr Ile Arg Gly Phe Arg
    705                 710                 715

gga atc cgt ctc cca gac tgg atg aat cac tca gtt ttg aaa aat gtt     3645
Gly Ile Arg Leu Pro Asp Trp Met Asn His Ser Val Leu Lys Asn Val
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gtc tct att gaa atc atc agt tgc aaa aac tgc tca tgc tta cca ccc     3693
Val Ser Ile Glu Ile Ile Ser Cys Lys Asn Cys Ser Cys Leu Pro Pro
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Phe Gly Glu Leu Pro Cys Leu Lys Ser Leu Glu Leu Trp Arg Gly Ser
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gcg gaa gtg gag tat gtt gat tct gga ttc cct aca aga aga agg ttt     3789
Ala Glu Val Glu Tyr Val Asp Ser Gly Phe Pro Thr Arg Arg Arg Phe
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Pro Ser Leu Arg Lys Leu Asn Ile Arg Glu Phe Asp Asn Leu Lys Gly
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Leu Leu Lys Lys Glu Gly Glu Glu Gln Cys Pro Val Leu Glu Glu Ile
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gag att aaa tgt tgc cct atg ttt gtt att cca acc ctt tct tct gtc     3933
Glu Ile Lys Cys Cys Pro Met Phe Val Ile Pro Thr Leu Ser Ser Val
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Lys Lys Leu Val Val Ser Gly Asp Lys Ser Asp Ala Ile Gly Phe Ser
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Ser Ile Ser Asn Leu Met Ala Leu Thr Ser Leu Gln Ile Arg Tyr Asn
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Lys Glu Asp Ala Ser Leu Pro Glu Glu Met Phe Lys Ser Leu Ala Asn
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Leu Lys Tyr Leu Asn Ile Ser Phe Tyr Phe Asn Leu Lys Glu Leu Pro
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acc agc ctg gct agt ctc aat gct ttg aag cat ctg gaa att cat agt     4173
Thr Ser Leu Ala Ser Leu Asn Ala Leu Lys His Leu Glu Ile His Ser
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Cys Tyr Ala Leu Glu Ser Leu Pro Glu Glu Gly Val Lys Gly Leu Ile
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Ser Leu Thr Gln Leu Ser Ile Thr Tyr Cys Glu Met Leu Gln Cys Leu
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ccg gag gga ttg cag cac cta aca gcc ctc aca aat tta tca gtt gag     4317
Pro Glu Gly Leu Gln His Leu Thr Ala Leu Thr Asn Leu Ser Val Glu
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ttt tgt cca aca ctg gcc aag cgg tgt gag aag gga ata gga gaa gac     4365
Phe Cys Pro Thr Leu Ala Lys Arg Cys Glu Lys Gly Ile Gly Glu Asp
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Lys Leu Gln Ser Thr Phe Thr Thr Ile Gln Ala Val Leu Glu Asp Ala
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Gln Lys Lys Gln Leu Lys Asp Lys Ala Ile Glu Asn Trp Leu Gln Lys
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Leu Asn Ala Ala Ala Tyr Glu Ala Asp Asp Ile Leu Asp Glu Cys Lys
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Thr Glu Ala Pro Ile Arg Gln Lys Lys Asn Lys Tyr Gly Cys Tyr His
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Pro Asn Val Ile Thr Phe Arg His Lys Ile Gly Lys Arg Met Lys Lys
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Ile Met Glu Lys Leu Asp Val Ile Ala Ala Glu Arg Ile Lys Phe His
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Leu Asp Glu Arg Thr Ile Glu Arg Gln Val Ala Thr Arg Gln Thr Gly
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Phe Val Leu Asn Glu Pro Gln Val Tyr Gly Arg Asp Lys Glu Lys Asp
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Glu Ile Val Lys Ile Leu Ile Asn Asn Val Ser Asn Ala Gln Thr Leu
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Pro Val Leu Pro Ile Leu Gly Met Gly Gly Leu Gly Lys Thr Thr Leu
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Ala Gln Met Val Phe Asn Asp Gln Arg Val Ile Glu His Phe His Pro
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Lys Ile Trp Ile Cys Val Ser Glu Asp Phe Asn Glu Lys Arg Leu Ile
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Lys Glu Ile Val Glu Ser Ile Glu Glu Lys Ser Leu Gly Gly Met Asp
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Tyr Leu Leu Val Leu Asp Asp Val Trp Asn Glu Asp Gln Asp Lys Trp
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Ala Lys Leu Arg Gln Val Leu Lys Val Gly Ala Ser Gly Ala Ser Val
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Leu Thr Thr Thr Arg Leu Glu Lys Val Gly Ser Ile Met Gly Thr Leu
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Gln Pro Tyr Glu Leu Ser Asn Leu Ser Gln Glu Asp Cys Trp Leu Leu
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Val Ala Ile Gly Lys Glu Ile Val Lys Lys Cys Gly Gly Val Pro Leu
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Glu Ser Ser Ile Leu Pro Ala Leu Arg Leu Ser Tyr His His Leu Pro
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Val Trp Asn Glu Leu Tyr Leu Arg Ser Phe Phe Gln Glu Ile Glu Val
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Lys Ser Gly Gln Thr Tyr Phe Lys Met His Asp Leu Ile His Asp Leu
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Ala Thr Ser Leu Phe Ser Ala Ser Thr Ser Ser Ser Asn Ile Arg Glu
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Ile Gly Asp Leu Val His Leu Arg Tyr Leu Asn Leu Ser Gly Asn Thr
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Ser Ile Arg Ser Leu Pro Asn Gln Leu Cys Lys Leu Gln Asn Leu Gln
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Ala Lys Glu Asn Leu His Ser Leu Ser Met Lys Trp Asp Asp Asp Glu
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Arg Pro Arg Ile Tyr Glu Ser Glu Lys Val Glu Val Leu Glu Ala Leu
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Glu Gly Leu Gln His Leu Thr Ala Leu Thr Asn Leu Ser Val Glu Phe
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Cys Pro Thr Leu Ala Lys Arg Cys Glu Lys Gly Ile Gly Glu Asp Trp
965 970 975

Tyr Lys Ile Ala His Ile Pro Arg Val Phe Ile Tyr
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